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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| **In re:** | **U.S. Patent No. 5,654,301** |
| Inventor: | KOHN, Harold et al. |
| Issue Date: | August 5, 1997 |
| For: | AMINO ACID DERIVATIVE ANTICONVULSANT |
| Assignee: | Research Corporation Technologies, Inc. |
| Date: | December 23, 2008 |
| Attorney Docket: | 32555-0002-2 |
| **NDA:** | **NDA 22-254 (VIMPAT® injection)** |

**Mail Stop Hatch-Waxman PTE**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**TRANSMITTAL FOR APPLICATION FOR EXTENSION OF PATENT**

Sir:

Transmitted herewith for filing is an Application For Extension of Patent Term Under 35 U.S.C. §156 with respect to the above-identified patent.

Applicant, the assignee of the above-referenced patent, on this day has filed simultaneously four related applications for extension of patent term under 35 U.S.C. §156, including the present application referenced in the header above. These four patent term extension applications relate to different combinations of U.S. Patent nos. Re38,551 and 5,654,301 and FDA approvals for New Drug Application nos. NDA 22-253 and NDA 22-254. The four patent term extension applications are summarized in the following table.

| Attorney Docket No. | Patent No. | NDA No. | Approved Product |
|---|---|---|---|
| 32555-0002-1 | Re38,551 | NDA22-253 | VIMPAT® (lacosamide) tablet |
| 32555-0002-2 | 5,654,301 | NDA 22-254 | VIMPAT® (lacosamide) injection |
| 32555-0002-3 | Re38,551 | NDA 22-254 | VIMPAT® (lacosamide) injection |
| 32555-0002-4 | 5,654,301 | NDA 22-253 | VIMPAT® (lacosamide) tablet |

Applicant asserts that it has the right, under 35 U.S.C. § 156, to extend two patents relating to VIMPAT® (lacosamide) because two NDAs, NDA 22-253 and NDA 22-254 for VIMPAT® (lacosamide) tablet and VIMPAT® (lacosamide) injection, respectively, were approved on the same day, namely October 28, 2008, and because there were no approvals of lacosamide that occurred prior to October 28, 2006. As such, Applicant has submitted the above four applications for patent term extension with the goal of ultimately obtaining one patent term extension for each of U.S. Patent nos. Re38,551 and 5,654,301.

Applicant respectfully requests that if the Commissioner determines that both of U.S. Patent nos. Re38,551 and 5,654,301 are entitled to a patent term extension under the same regulatory review period or periods (i.e., for the same NDA(s)), and/or determines that at least one of U.S. Patent nos. Re38,551 and 5,654,301 is entitled to a patent term extension under both regulatory review periods (i.e., for both of the two NDA approvals), that the Commissioner establish a time period in accord with the policies set forth in MPEP § 2761 within which the Applicant will be permitted to elect the patent and product combination(s) for which extension is desired and/or to voluntarily withdraw applications. At that time, Applicant will elect and withdraw applications for patent term extension, as appropriate, to ensure that only one patent is extended for each NDA, and such that a given patent obtains only one extension under 35 U.S.C. § 156.

Applicant respectfully requests that if the Commissioner does not share Applicant's view that it is entitled under 35 U.S.C. § 156 to extend a different patent for each of the two above-identified simultaneously-approved NDAs, that the Commissioner direct the Office to contact the undersigned attorney.

In light of the above, and in accordance with the requirements of 35 U.S.C. § 156, attached for the patent and NDA approval identified in the above header are the following:

1) Application For Extension of Patent Term (including Exhibits A-F) – application 15 pages and Exhibits 155 pages for 170 pages total;

2) Extra copy 1 of Application for Extension of Patent Term (including Exhibits A-F) – application 15 pages and Exhibits 155 pages for 170 pages total; and

3) Extra copy 2 of Application for Extension of Patent Term (including Exhibits A-F) – application 15 pages and Exhibits 155 pages for 170 pages total.

☒ Please charge my Deposit Account No. 50-1349 the amount of $1,120.00, which is believed to be the appropriate fee for a patent term extension as established by 37 C.F.R. § 1.20(j),.

☒ The Commissioner is hereby authorized to charge payment of any fees associated with or necessary for the prosecution of this patent term extension application, including debiting any deficit or crediting any overpayment relating to the fee identified above, to Deposit Account No. 50-1349.

Respectfully submitted,

**HOGAN & HARTSON LLP**

Dated: December 23, 2008

By: _____
Kevin G. Shaw
Registration No. 43,110

**HOGAN & HARTSON LLP**
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Facsimile: 202-637-5910
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**Customer No. 24633**


**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| **In re:** | **U.S. Patent No. 5,654,301** |
| Inventor: | KOHN, Harold et al. |
| Issue Date: | August 5, 1997 |
| For: | AMINO ACID DERIVATIVE ANTICONVULSANT |
| Assignee: | Research Corporation Technologies, Inc. |
| Date: | December 23, 2008 |
| Attorney Docket: | 32555-0002-2 |
| **NDA:** | **NDA 22-254 (VIMPAT® injection)** |

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. §156

Commissioner for Patents:

Applicant, Research Corporation Technologies, Inc., a non-profit corporation organized and existing under the laws of Delaware, and having a principal place of business at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410, represents that it is the owner of the entire interest in and to U.S. Patent No. 5,654,301, granted to Harold Kohn and Darrell Watson for "Amino Acid Derivative Anticonvulsant," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on January 12, 1993 at Reel 006433, Frame 0347. Attached at **Exhibit A** is a Power of Attorney document appointing the undersigned patent attorney as legal representative of Applicant.

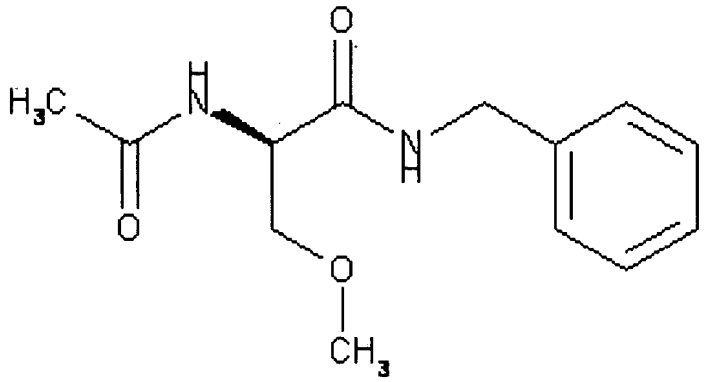
Schwarz Biosciences, Inc. ("Schwarz"), a corporation of the state of Delaware and having a place of business at 1209 Orange St., Wilmington, DE 19801, is the owner of a New Drug Application ("NDA") for VIMPAT® injection, NDA number NDA 22-254. Schwarz

Pharma AG ("SPAG"), having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany, has exclusive license rights under U.S. Patent No. 5,654,301 to lacosamide, R-2-Acetamido-N-benzyl-3-methoxypropionamide. Schwarz and SPAG are related companies, being wholly owned by UCB S.A., which has its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium. Attached at **Exhibit B** is a Letter of Reliance document granting to the Applicant from Schwarz the right to rely upon NDA 22-254 and the activities of SPAG and its predecessors in interest supporting FDA approval of VIMPAT® injection for purposes of obtaining any and all patent term extensions available in conjunction with the approval of VIMPAT® injection.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156, based upon the approval by the Food and Drug Administration for commercial marketing or use of VIMPAT® injection, since the active ingredient of VIMPAT® injection is lacosamide and lacosamide falls within the ambit of the claims of U.S. Patent No. 5,654,301. The information contained in this Application and its Exhibits is provided in accordance with the rules promulgated by the U.S. Patent and Trademark Office at 37 CFR §§1.710-1.785 and presented in the manner set forth at 37 CFR §1.740.

1. A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product, VIMPAT® injection, contains lacosamide as its active ingredient and is indicated for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible. The IUPAC chemical name of lacosamide is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. Lacosamide has the empirical formula $C_{13}H_{18}N_2O_3$, and has a molecular weight of 250.30. Lacosamide is present in VIMPAT® injection in the form of a single (R)-enantiomer, and has the structural formula:



Lacosamide is prepared as a white to light yellow powder that is sparingly soluble in acetonitrile and ethanol. The approved product is formulated for intravenous injection as a clear, colorless, sterile solution containing 10 mg lacosamide per mL for intravenous infusion. One 20 mL vial contains 200 mg of lacosamide, plus inactive ingredients sodium chloride and water for injection. Hydrochloric acid is used for pH adjustment, giving VIMPAT® injection a pH of 3.5 to 5.0. The initial recommended dosage regimen is 100 mg of lacosamide infusion per day, and dosage can be increased, such as at weekly intervals of 100 mg/day, until a maintenance dose of 200 to 400 mg/day (based upon individual patient response and tolerability) is reached.

2. A Complete Identification Of The Federal Statute Including The Applicable Provisions Of Law Under Which The Regulatory Review Occurred

The approved product, VIMPAT® injection, was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355).

3. An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

The approved product, VIMPAT® injection, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) on October 28, 2008. A copy of a letter from the Food and Drug Administration ("FDA") indicating the date of approval is attached hereto at **Exhibit C**.

4. In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, and Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The active ingredient in VIMPAT® injection is lacosamide, which has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to 37 CFR §1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is December 26, 2008.

6. A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of The Inventor, The Patent Number, The Date Of Issue, And The Date Of Expiration

The complete identification of the patent for which extension is sought is:

| | |
|---|---|
| Inventors: | Harold Kohn, and Darrell Watson |
| Patent Number: | 5,654,301 |
| Issue Date: | August 5, 1997 |
| Expiration Date: | August 5, 2014 (without extension under 35 U.S.C. §156) |

7. A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A complete copy of U.S. Patent No. 5,654,301 is annexed as **Exhibit D**.

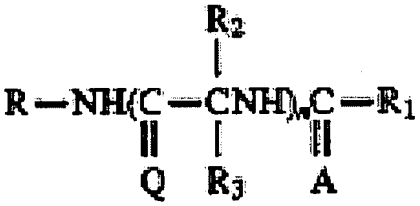
8. A Copy Of Any Disclaimer, Certificate of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In The Patent

The patent for which extension is being sought has not been the subject of any disclaimer or reexamination certificate, but has had a certificate of correction duly issued by the

U.S. Patent and Trademark Office. A copy of the certificate of correction, dated November 27, 2001, is included at the end of the copy of U.S. Patent No. 6,654,301 annexed as **Exhibit D**. The first two scheduled maintenance fees for U.S. Patent 5,654,301 were duly paid on February 2, 2001 and December 3, 2004 by Applicant, and the next maintenance fee is due to be paid by February 6, 2009. Copies of the maintenance fee statements evidencing past payments are annexed as **Exhibit E**.

9. A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which At Least One Such Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

U.S. Patent No. 5,654,301 claims the approved product, VIMPAT® injection. More specifically, claims 39-45 read on the approved product and claim the active ingredient of the final approved product lacosamide, claim 46 reads on the approved product and claims a composition comprising lacosamide, and claim 47 reads on methods that comprise using lacosamide for treatment of CNS (i.e., central nervous system) disorders. Claim 39, covering a compound, is compared to the approved product in the table below.

| Patent Claim | Approved Product |
|---|---|
| 39. A compound of the formula  or the pharmaceutically acceptable salts thereof wherein R is aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl or lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron | The active ingredient of the approved product is lacosamide, which is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. Lacosamide has the structural formula identified above in Section 1 of this application. Comparison of the structural formula above with that in claim 39 shows that the benzyl group at the far right of the structural formula identified above in Section 1 is an unsubstituted aryl lower alkyl and thus satisfies the claim's definition of "R." The $-CH_3$ group at the far left of the structure in Section 1 is a lower alkyl that satisfies the claim's definition of "$R_1$." The two double-bonded oxygen atoms satisfy |

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| withdrawing group or an electron donating group;<br><br>$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;<br><br>A and Q are both O;<br><br>one of $R_2$ and $R_3$ is hydrogen and the other is lower alkyl which is substituted with an electron donating group or a electron withdrawing group and n is 1-4. | the claim's definition of both "A" and "Q." The central chiral carbon atom is bonded to a hydrogen and a -$CH_2OCH_3$ group (a lower alkyl substituted with a methoxy group), thus satisfying the claim's requirement that one of $R_2$ and $R_3$ be a hydrogen while the other of $R_2$ and $R_3$ is a lower alkyl substituted with an electron donating group. A lower alkoxy, such as a -$OCH_3$ group, is defined by dependent claim 43 and the specification as a suitable electron donating group. Lacosamide qualifies as a chemical defined by claim 39 when n is equal to 1. |

Claim 46, covering a therapeutic composition, is compared to the approved product in the table below.

| **Patent Claim** | **Approved Product** |
|---|---|
| 46. An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim 37-42 and a pharmaceutical carrier therefor. | The active ingredient of the approved product is lacosamide, and lacosamide falls within the scope of claim 39 as indicated above. The approved product is a composition for intravenous injection that contains a pharmaceutical carrier, water and sodium chloride. |

Claim 47, covering a method of treating central nervous system disorders, is compared to the approved product and its indicated use in the table below.

| **Patent Claim** | **Approved Product** |
|---|---|
| 47. A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of any one of claims 39- | The active ingredient of the approved product is lacosamide, and lacosamide falls within the scope of claim 39 as indicated above. Lacosamide is an anticonvulsant approved for the treatment of partial- |

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| 44. | onset seizures in patients with epilepsy, which is a central nervous system ("CNS") disorder. |

10. A Statement, Beginning On A New Page, Of The Relevant Dates And Information Pursuant To 35 U.S.C. § 156(g) In Order To Enable The Secretary Of Agriculture, As Appropriate, To Determine The Applicable Regulatory Review Period As Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, Or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) Or A Product License Application (PLA) Was Initially Submitted And The NDA Or PLA Number And The Date On Which The NDA Was Approved Or The Product License Issued

Schwarz Biosciences, Inc. was notified via telephone that the IND for VIMPAT® injection (IND 68,407) became effective on November 14, 2003, and received a letter dated December 24, 2003 from the FDA confirming that IND 68,407 became effective on that earlier date. For purposes of this application for patent term extension, the Applicant is entitled to an IND date of at least as early as November 14, 2003.[1] The NDA (NDA 22-254) for VIMPAT® injection was initially submitted to the Food and Drug Administration on September 28, 2007 and was approved on October 28, 2008.

[1] A predecessor in interest to Schwarz, Harris FRC Corp., previously filed IND 57,939 for VIMPAT® (lacosamide) tablet. IND 57,939 became effective on May 19, 1999, and was followed by NDA 22-253 on September 28, 2007. NDA 22-253 was approved on October 28, 2008 for VIMPAT® (lacosamide) tablet. Both NDA approvals (for NDA 22-253 and NDA22-254) rely upon the same Phase I safety & tolerance studies for lacosamide. (See Exhibit F, page 1 for "IND 68,407 Submissions" chart indicating on October 15, 2003 a cross-referencing was made to "all preclinical and clinical reports from oral IND"). Applicant understands that, where multiple INDs are in effect, and data from such multiple INDs was material to the determination to approve the product, it is the policy of the FDA to consider whether it would be appropriate to define the testing phase as having begun when the first IND became effective. Applicant therefore submits that an earlier IND effective date, namely May 19, 1999, may be appropriate for use in calculating the full term of the regulatory review period for this patent term extension application. Applicant will supplement this application with additional information concerning IND 57,939 and/or NDA 22-253 upon request by the Patent Office and/or the FDA.

11. A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A brief description of significant activities undertaken by the marketing applicant during the regulatory review period with respect to the approved product is annexed as **Exhibit F**. This exhibit provides a chronology of the major communications between the marketing applicant and the Food and Drug Administration, including a brief summary of the subject matter and date of these communications.

Applicant reserves the right to supplement the chronology of **Exhibit F** with materials from which it was derived or other evidence related to Applicant's conduct in obtaining the approval of VIMPAT® injection. *See, e.g.*, 21 CFR § 60.32.

12. A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Applicant is of the opinion that U.S. Patent No. 5,654,301 is eligible for extension under 35 U.S.C. § 156, because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. §156(a); 37 CFR §1.720(a)

U.S. Patent No. 5,654,301 claims a product, and a method of using a product.

b. 35 U.S.C. §156(a)(1); 37 CFR §1.720(g)

The term of U.S. Patent No. 5,654,301 has not expired before submission of this application.

c. 35 U.S.C. §156(a)(2); 37 CFR §1.720(b)

The term of U.S. Patent No. 5,654,301 has never previously been extended under 35 U.S.C. §156.

d. 35 U.S.C. §156(a)(3); 37 CFR §1.730

This application for extension is submitted by the authorized agent or the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. §156(a)(4); 37 CFR §1.720(d)

The product VIMPAT® injection has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use.

f. 35 U.S.C. §156(a)(5)(A); 37 CFR §1.720(e)(i)

The commercial marketing or use of the product VIMPAT® injection after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetics Act (21 U.S.C. §360) under which such regulatory review period occurred.

g. 35 U.S.C. §156(c)(4); 37 CFR §1.720(h)

No other patent has been extended for the same regulatory review period for the product VIMPAT® injection.

h. 35 U.S.C. §156(d)(1); 37 CFR §1.720(f)

This application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

Applicant is of the opinion that U.S. Patent No. 5,654,301 is eligible for extension under 35 U.S.C. § 156 for 1104 days, as determined pursuant to 37 CFR §1.775 as follows:

Patent Information:

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| Patent 5,654,301 Issue Date | August 5, 1997 |
| Earliest non-provisional priority date | February 15, 1985 |
| Days Extension under 35 U.S.C. 154(b) | 0 |

FDA Information:

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| Date IND Became Effective | November 14, 2003 |
| Date NDA Submitted to the FDA | September 28, 2007 |
| Date NDA Approved by the FDA | October 28, 2008 |

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| IND Period: | |
| Start Date of Regulatory Review Period | November 14, 2003 |
| IND Period (days) | 1414 |
| ½ IND Period (days) | 707 |
| Regulatory Review Period Allowed: | |
| NDA Review Period (days) | 397 |
| Regulatory Review Period (days) | 1811 |
| Reg. Rev. Period less ½ IND period (days) | 1104 |
| Statutory Limitations: | |
| Patent Expiration Date (17 year term) | August 5, 2014 |
| Expiration under 5 year extension limitation (Date 1) | August 5, 2019 |
| Expiration under 14 from NDA approval limitation (Date 2) | October 28, 2022 |
| Expiration based upon full review period (Date 3) | August 13, 2017 |
| Final Expiration Date (Earliest of Date 1, Date 2, or Date 3) | August 13, 2017 |
| Maximum Extension in Days: | **1104**[2] |

[2] All calculations above are performed assuming that November 14, 2003 is the appropriate date for when the relevant regulatory review period started. As noted above in footnote 1 on page 8, it is possible that the FDA could determine that a date as early as May 19, 1999 is the appropriate date for the start of the regulatory review period. Should that earlier date, or another earlier date, in fact be the appropriate start date for the regulatory review period, then Applicant would be entitled to a longer calculated review period, and thus a later "Date 3" above. For example, should the applicable regulatory review period be determined to have started on May 19, 1999, then the IND period will have lasted 3054 days, and the full regulatory review period will have lasted 3451 days. Thus, the regulatory review period less ½ IND period as calculated would be 1924 days. This would make the expiration of patent no. 5,654,301 based upon the full regulatory review period (Date 3) be November 11, 2019. In this scenario, Applicant would be entitled to a full five-year extension of patent no. 5,654,301, making it expire August 5, 2019 (i.e, Date 1 above).

13. A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

14. The Prescribed Fee For Receiving And Acting Upon The Application For Extension

The prescribed fee pursuant to 37 CFR §1.20(j) for receiving and acting upon this application is to be charged to the Deposit Account of Applicant's undersigned attorney as authorized in the attached letter.

15. The Name, Address, And Telephone Number Of The Person To Whom Inquiries And Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

Kevin G. Shaw
Hogan & Hartson, LLP
555 Thirteenth St., NW
Washington, DC 20004

16. A Duplicate Of The Application Papers, Certified As Such

Applicant hereby certifies that this application for extension is being filed in triplicate.

17. An Oath Or Declaration

Applicant, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the agent or owner to act on behalf of the agent or owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States

Code and that willful false statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to an extension pursuant to 37 C.F.R. § 1.710 in the event of NDA approval and, in the interim, is subject to an extension pursuant to 37 C.F.R. § 1.790;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

(5) The undersigned believes the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720 in the event of NDA approval, and meets the requirements for an interim extension of a patent set forth in 37 C.F.R. § 1.790.

If this application for extension of patent term is held to be informal, applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

Dated: December 23, 2008

By: _____
Kevin G. Shaw
Registration No. 43,110

**HOGAN & HARTSON LLP**
555 13th Street, N.W.
Washington, D.C. 20004
Telephone: 202-637-5600
Facsimile: 202-637-5910
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Customer No.: 24633

# Exhibit A

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| In re: | U.S. Patent No. 5,654,301 |
| Inventor: | KOHN, Harold et al. |
| Issue Date: | August 5, 1997 |
| For: | AMINO ACID DERIVATIVE ANTICONVULSANT |
| Assignee: | Research Corporation Technologies, Inc. |
| Attorney Docket: | 32555-0002-2 |

POWER OF ATTORNEY FOR PATENT TERM EXTENSION APPLICATION

Research Corporation Technologies, Inc., a non-profit corporation organized and existing under the laws of Delaware, and having a principal place of business at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410, represents that it is the owner of the entire interest in and to U.S. Patent No. 5,654,301, granted to Harold Kohn and Darrell Watson for "Amino Acid Derivative Anticonvulsant," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on January 12, 1993 at Reel 006433, Frame 0347.

Research Corporation Technologies, Inc. hereby revokes all previous powers of attorney and appoints Kevin G. Shaw and the registered practitioners of Hogan & Hartson, L.L.P. included in the Customer Number provided below to prosecute this patent term extension application and to transact all business in the Patent and Trademark Office connected therewith, and further directs that all correspondence be addressed to Kevin G. Shaw at that Customer Number. The undersigned, acting in the official capacity stated below, has authority to does hereby execute this document on behalf of Research Corporation Technologies, Inc.

**Customer Number: 24633**

Please direct all inquiries to:

Kevin G. Shaw
Telephone: (202) 637-6466
Facsimile: (202) 637-5910

Shaun A. Kirkpatrick

December 17, 2008
Date

President & CEO
Research Corporation Technologies, Inc.
5210 E. Williams Circle, Suite 240
Tucson, AZ
85711-4410

# Exhibit B

SCHWARZ
PHARMA
A member of the UCB Group, Inc.

**LETTER OF RELIANCE**

**Mail Stop Hatch-Waxman PTE**
**Office of Patent Legal Administration**
**Room MDW 7D55**
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**Alexandria, VA 22314**

**Attn: Mary C. Till, Examiner**
**Office of Patent Legal Administration**

**Schwarz Biosciences, Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA; "SBI") is directly held by UCB Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA), the latter being a directly and indirectly wholly-owned subsidiary of UCB Holdings, Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA) which is directly wholly-owned subsidiary of UCB S.A. (having its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium).**

**Schwarz Pharma AG (having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany; "SPAG") is directly held by UCB SP GmbH (having an office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany) which is a directly wholly-owned subsidiary of UCB GmbH (having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany), the latter being directly and indirectly held by UCB S.A. (having its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium).**

**SPAG has exclusive license rights regarding lacosamide, R-2-Acetamido-N-benzyl-3-methoxypropionamide, under U.S. Patent Nos. Re38,551 and 5,654,301, as sublicensee of Harris FRC Corporation (having an office at 2137 Route 35 Holmdel, New Jersey 07733; "Harris FRC") that is licensee from Research Corporation Technologies, Inc. (having an office at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410; "RCT"). Hence, SPAG, Harris FRC, and RCT are sublicensee, licensee and assignee, respectively, of U.S. Patent Nos. Re38,551 and 5,654,301.**

**SBI, as NDA holder, authorizes RCT to rely on activities of SBI and its predecessors in interest relating to FDA approval of VIMPAT® lacosamide products as adjunctive therapy in treatment of partial-onset seizures in patients with epilepsy, in Tablet form under NDA 22-253 and in Injection form under NDA 22-254, in support of RCT's intension to apply for extension of patent term of U.S. Patent Nos. Re38,551 and 5,654,301,as provided under 35 U.S.C. §156(d) (1), 37 C.F.R. §1.730 and MPEP 2752.**

*SCHWARZ BIOSCIENCES, Inc. A member of the UCB Group, Inc.*
*Mail P.O. Box 110167 · Research Triangle Park · NC 27709 · Via Courier 8010 Arco Corporate Drive · Suite 100 · Raleigh · NC 27617 · USA*
*Phone +1 919 767 2555 · Toll Free +1 866 724 2467 · Fax +1 919 767 2570 · www.schwarzpharma.com · www.ucb-group.com*

SCHWARZ
PHARMA

Authorized by Schwarz Biosciences, Inc.

By: Patricia A. Hartz for Deborah Hogerman Date: 12-01-08

Deborah Hogerman
Senior Director, U.S. Regulatory Affairs
On behalf of Schwarz Biosciences, Inc.

cc: Research Corporation Technologies, Inc.
cc: Harris FRC Corporation

# Exhibit C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**NDA APPROVAL**

NDA 22-253
NDA 22-254

Schwarz Biosciences, Inc.
Attention: Alan Blumberg
Senior Director, US Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Mr. Blumberg:

Please refer to your new drug applications (NDAs) dated September 28, 2007, received September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vimpat (lacosamide) Tablets, 50 mg, 100 mg, 150 mg, and 200 mg, and Vimpat (lacosamide) Injection, 200 mg per 20 ml.

We acknowledge receipt of your additional submissions dated:

| | | | | |
|---|---|---|---|---|
| November 26, 2007 | March 20, 2008 | April 30, 2008 | July 17, 2008 | September 4, 2008 |
| December 13, 2007 | April 3, 2008 | May 9, 2008 | July 30, 2008 | September 23, 2008 |
| January 23, 2008 | April 9, 2008 | May 27, 2008 | August 1, 2008 | October 15, 2008 |
| February 13, 2008 | April 14, 2008 | June 11, 2008 | August 14, 2008 | October 21, 2008 |
| February 22, 2008 | April 18, 2008 | July 11, 2008 (2) | August 27, 2008 | |

These new drug applications provide for the use of Vimpat (lacosamide) as follows:

- Vimpat (lacosamide) Tablets as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

- Vimpat (lacosamide) Injection as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your applications for Vimpat (lacosamide) Tablets and Injection (NDA 22-253, 22-254) were not referred to an FDA advisory committee because your products are members of the class of previously approved anti-epileptic drugs and the products did not pose unique concerns beyond those applicable to other members of this class.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 1 month for these applications because necessary studies are impossible or highly impracticable because there are too few children with partial onset seizures in this age group to study.

In addition, we are deferring submission of your pediatric studies in partial onset seizures for ages 1 month up to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Deferred pediatric studies under PREA for the adjunctive treatment of partial onset seizures in pediatric patients ages 1 month up to 17 years.

   Final Report Submission: July 2013

Submit final study reports to these NDAs. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment.**"

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Vimpat (lacosamide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is

necessary for patients' safe and effective use of Vimpat (lacosamide). FDA has determined that Vimpat (lacosamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Vimpat (lacosamide). In addition, patient labeling could help prevent serious adverse effects related to the use of these products. Vimpat (lacosamide) may increase the risk of suicidal thoughts or behavior in patients taking anti-epileptic drugs for any indication. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Vimpat (lacosamide).

Your proposed REMS, submitted on October 17, 2008, in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 17, 2008 submission.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 22-253 & 22-254 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 22-253 & 22-254**
  **PROPOSED REMS MODIFICATION**
  **< other supplement identification > [if included]**
  **<REMS ASSESSMENT> [if included]**

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of developmental neurotoxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

2. A nonclinical study in rats to examine the effects of Vimpat (lacosamide) on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing central nervous system structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.

The timetable you have submitted on October 28, 2008 states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Protocol Submission: | Within 6 months of approval |
| Final Report Submission: | Within 30 months of approval |

Submit protocols to your IND 57,939 with a cross-reference letter to these new drug applications (NDA) 22-253 and 22-254. Submit final reports to your NDAs 22-253 and 22-254. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS

We acknowledge your written commitment to conduct the following postmarketing study as described in your submission dated October 28, 2008, as outlined below:

3. *In vitro* data to determine which enzymes may be involved in the metabolism of Vimpat (lacosamide) in addition to CYP2C19.

| | |
|---|---|
| Final Report Submission: | within 18 months of approval |

Submit the protocol to your IND (b)(4). Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled:

- **Postmarketing Study Commitment Protocol**
- **Postmarketing Study Commitment Final Report**
- **Postmarketing Study Commitment Correspondence**

## HIGHLIGHTS WAIVER

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 22-253 and NDA 22-254."**

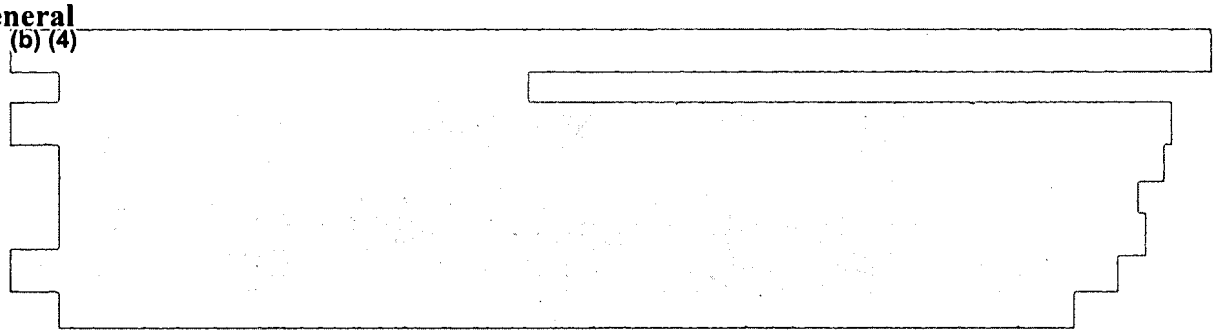
## CARTON AND IMMEDIATE CONTAINER LABELS

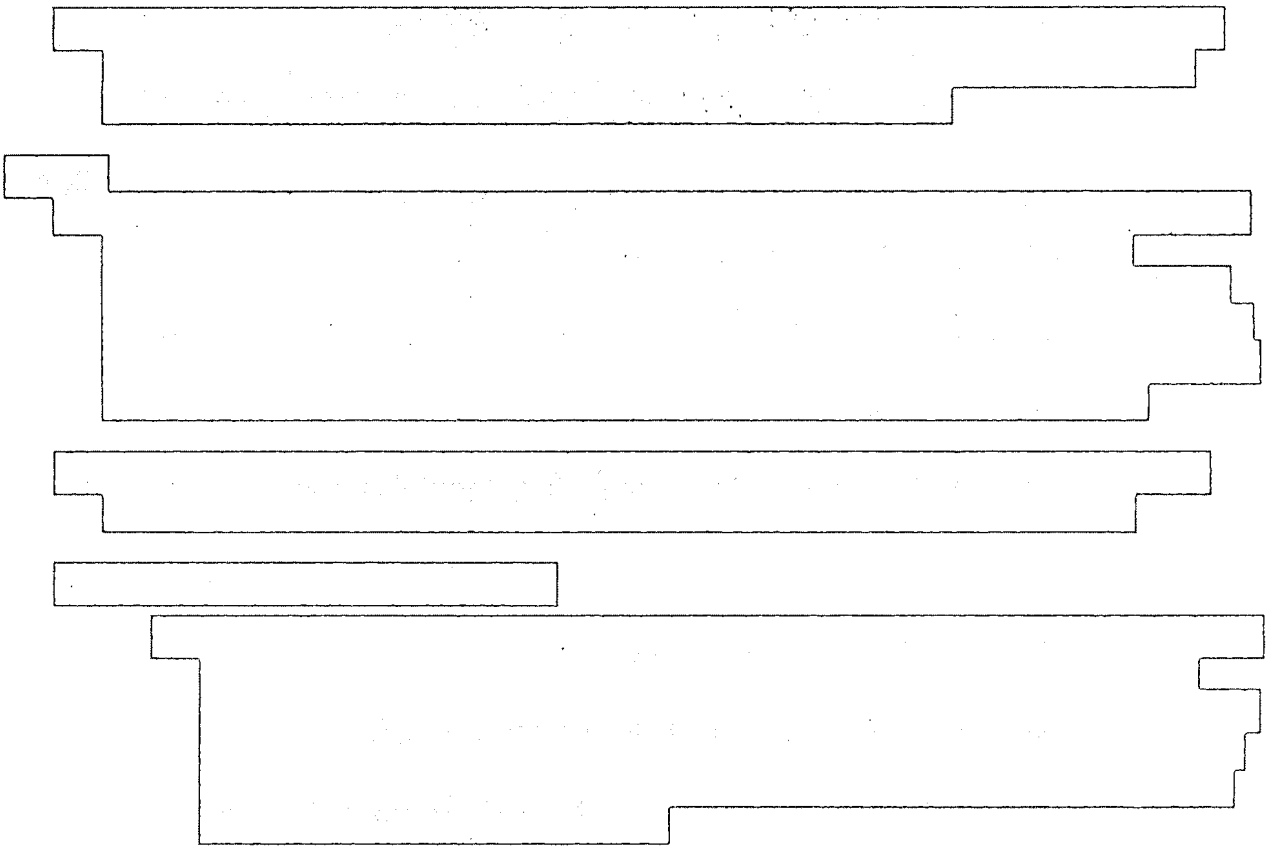
Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-253 and NDA 22-254**" Approval of this submission by FDA is not required before the labeling is used.

In addition, we note your agreement on October 28, 2008 to address and make the following changes into your carton and immediate container labels:

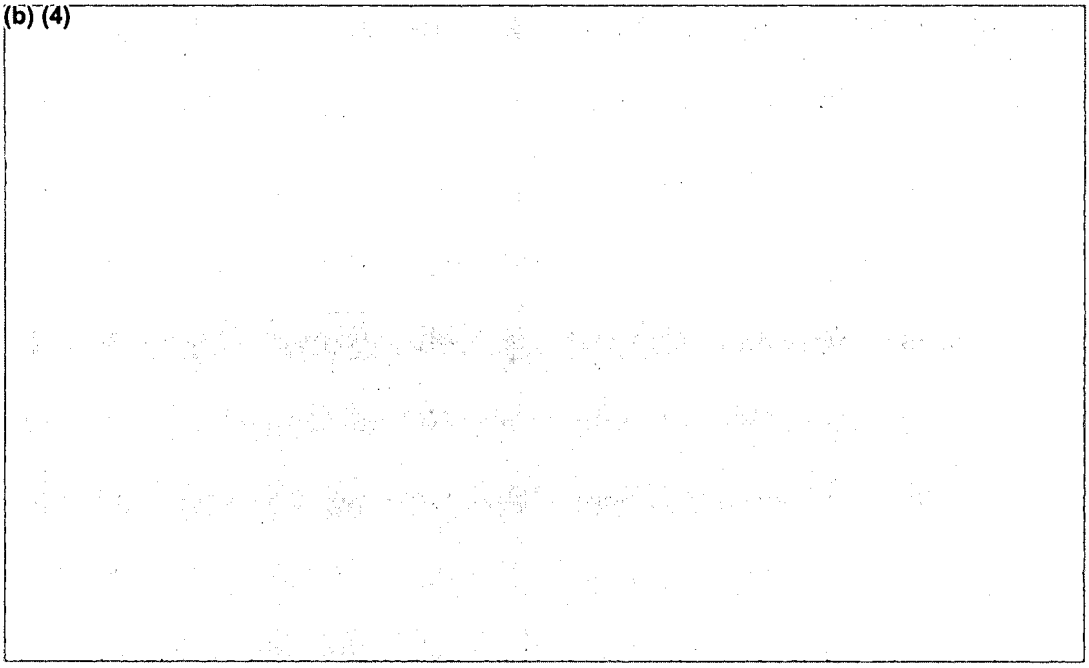
**General**

(b) (4)

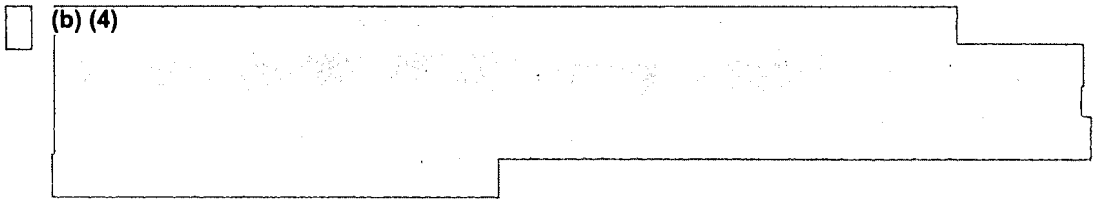




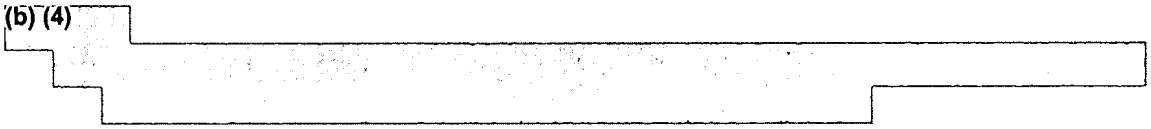
(b) (4)



(b) (4)



(b) (4)



Marketing the products with FPL that is not identical to the approved labeling text including the changes noted above may render the product misbranded and an unapproved new drug.

## CONTROLLED SUBSTANCE CLASS

We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule.

## EXPIRATION DATE (Injection)

We grant the proposed 36 month drug product expiry, when stored at controlled room temperature, for lacosamide 200 mg/20 mL injection packaged in 20 mL type I colorless glass vials with a grey rubber stopper coated with a (b) (4) and aluminum overseal.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

**MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Supervisory Regulatory Project Manager, at (301) 796-1160.

Sincerely,

*{See appended electronic signature page}*

Ellis F. Unger, M.D.
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures (FDA Approved Labeling Text, Medication Guide, and REMS document)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Ellis Unger

10/28/2008 08:00:13 PM

# Exhibit D

US005654301A

# United States Patent [19]

Kohn et al.

[11] Patent Number: 5,654,301

[45] Date of Patent: Aug. 5, 1997

[54] **AMINO ACID DERIVATIVE ANTICONVULSANT**

[75] Inventors: **Harold L. Kohn**, Houston; **Darrell Watson**, Belton, both of Tex.

[73] Assignee: **Research Corporation Technologies, Inc.**, Tucson, Ariz.

[21] Appl. No.: **3,208**

[22] Filed: **Jan. 12, 1993**

**Related U.S. Application Data**

[63] Continuation-in-part of Ser. No. 710,610, Jun. 4, 1991, Pat. No. 5,378,729, which is a continuation-in-part of Ser. No. 354,057, May 19, 1989, abandoned, and a continuation-in-part of Ser. No. 392,870, Aug. 11, 1989, abandoned, said Ser. No. 354,057, is a continuation-in-part of Ser. No. 80,528, Jul. 31, 1987, abandoned, which is a continuation-in-part of Ser. No. 916,254, Oct. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 702,195, Feb. 15, 1985, abandoned, said Ser. No. 392,870, is a continuation of Ser. No. 80,528, Jul. 31, 1987, abandoned, which is a continuation-in-part of Ser. No. 916,254, Oct. 7, 1986, abandoned, which is a continuation-in-part of Ser. No. 702,195, Feb. 15, 1985, abandoned.

[30] **Foreign Application Priority Data**

Jun. 4, 1992 [WO] WIPO ..... US92/04687

[51] **Int. Cl.**[6] ..... **A61K 31/445**; A61K 31/34; C07D 211/72; C07D 261/04

[52] **U.S. Cl.** ..... **514/231.2**; 514/315; 514/397; 514/406; 514/415; 514/424; 514/461; 514/468; 514/486; 514/616; 546/292; 548/125; 548/225; 548/250; 548/347.1; 548/245; 548/371.4; 564/152; 564/154; 564/292

[58] **Field of Search** ..... 564/148, 155, 564/154, 152; 548/125, 245, 371.4; 514/315, 357, 461, 406, 548, 424, 415, 549, 618, 486, 231.2; 546/252, 152, 154

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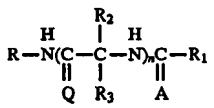
(List continued on next page.)

*Primary Examiner*—Theodore J. Criares

*Attorney, Agent, or Firm*—Scully, Scott, Murphy & Presser

[57] **ABSTRACT**

The present invention relates to compounds of the formula



**47 Claims, No Drawings**

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# AMINO ACID DERIVATIVE ANTICONVULSANT

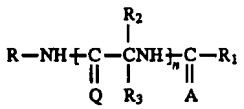
## RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. patent application Ser. No. 710,610 filed on Jun. 4, 1991, now U.S. Pat. No. 5,378,729 which is a continuation-in-part of U.S. patent application Ser. No. 354,057 filed on May 19, 1989, now abandoned and U.S. patent application Ser. No. 392,870 filed on Aug. 11, 1989, now abandoned. U.S. patent application Ser. No. 354,057 is a continuation-in-part of U.S. patent application having Ser. No. 080,528, filed on Jul. 31, 1987, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 916,254, filed Oct. 7, 1986, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 702,195, filed Feb. 15, 1985, now abandoned. U.S. patent application Ser. No. 392,870 is a continuation application of U.S. patent application having Ser. No. 080,528, filed Jul. 31, 1987, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 916,254 filed Oct. 7, 1986, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 702,195 filed on Feb. 15, 1985, now abandoned.

This invention was made with Government support under NS15604 awarded by the National Institutes of Health. The Government has certain rights to this invention.

## BACKGROUND OF THE INVENTION

The present invention relates to compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders. More specifically, the compounds of this invention can be characterized as protected amino acid derivatives of the formula:



I

or the N-oxides thereof or pharmaceutically acceptable salts thereof wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, loweralkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

$R_1$ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

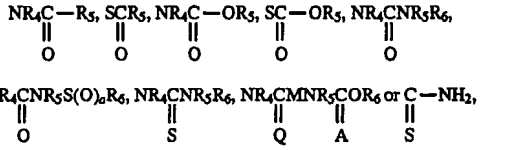
$R_2$ and $R_3$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, $SO_3^-$ or Z—Y wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S,$S(O)_a$, $NR_4$, $PR_4$ or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower alkyl and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided Z is a chemical bond only, when Y is halo, or



ZY taken together is $NR_4NR_5R_7$, $NR_4OR_5$, $ONR_4R_7$, $OPR_4R_5$, $PR_4OR_5$, $SNR_4R_7$, $NR_4SR_7$, $SPR_4R_5$, $PR_4SR_7$, $NR_4PR_5R_6$ $PR_4NR_5R_7$,



$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

$R_7$ is $R_6$ or $COOR_8$ or $COR_8$

$R_8$ is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

A and Q are independently O or S, M is an alkylene chain containing up to 6 carbon atoms or a chemical bond;

n is 1–4 and

a is 1–3.

The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with loss of consciousness.

The mainstay of treatment for such disorders has been the long-term and consistent administration of anticonvulsant drugs. Most drugs in use are weak acids that, presumably, exert their action on neurons, glial cells or both of the central nervous system. The majority of these compounds are characterized by the presence of at least one amide unit and one or more benzene rings that are present as a phenyl group or part of a cyclic system.

Much attention has been focused upon the development of anticonvulsant drugs and today many such drugs are well known. For example, the hydantions, such as phenytoin, are useful in the control of generalized seizures and all forms of partial seizures. The oxazolidinediones, such as trimethadione and paramethadione, are used in the treatment of nonconvulsive seizures. Phenacemide, a phenylacetylurea, is one of the most well known anticonvulsants employed today, while much attention has recently been dedicated to the investigation of the diazepines and piperazines. For example, U.S. Pat. Nos. 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified diazepine derivatives useful in the treatment of epilepsy and other nervous disorders. U.S. Pat. No. 3,887,543 to Nakanishi, et al. describes a thieno[2,3-e][1,4]diazepine compound also having anticonvulsant activity and other depressant activity. U.S. Pat. No. 4,209,516 to Heckendorn, et al. relates to triazole derivatives which exhibit anticonvulsant activity and are useful in the treatment of epilepsy and conditions of tension and agitation. U.S. Pat. No. 4,322,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administration of these compounds in an acid pH range are useful in the

treatment of convulsion disorders and also possess anxiolytic and sedative properties.

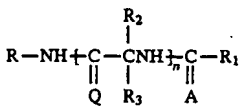
Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control and most have disturbing side-effects. Clearly, current therapy has failed to "seize control" of these debilitating diseases.

It is therefore one object of the present invention to provide novel compounds exhibiting CNS activity, particularly anticonvulsant activity.

Another object of this invention is to provide pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

A further object of this invention is to provide a method of treating epilepsy and related convulsant disorders.

These and other objects are accomplished herein by providing compounds of the following general formula:



wherein R, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, n, Z, Y, A and Q are as defined hereinabove.

The present invention contemplates employing the compounds of Formula I in compositions of pharmaceutically acceptable dosage forms. Where the appropriate substituents are employed, the present invention also includes pharmaceutically acceptable addition salts. Moreover, the administration of an effective amount of the present compounds, in their pharmaceutically acceptable forms or the addition salts thereof, can provide an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous disorders.

The alkyl groups when used alone or in combination with other groups, are lower alkyl containing from 1 to 6 carbon atoms and may be straight chain or branched. These groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl, hexyl, and the like.

The aryl lower alkyl groups include, for example, benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, and the like, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenylethyl, and the like.

The term aryl, when used along or in combination, refers to an aromatic group which contains from 6 up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatics. These aryl groups may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. Polynuclear aromatic compound is meant to encompass bicyclic, tricyclic fused aromatic ring system containing from 10–18 ring carbon atoms and up to a total of 25 carbon atoms. The aryl group includes phenyl, and the polynuclear aromatics e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like. The aryl group also includes groups like ferrocenyl.

Lower alkenyl is an alkenyl group containing from 2 to 6 carbon atoms and at least one double bond. These groups may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1-butenyl, isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentenyl, (Z)-4-methyl-2-pentenyl, (E-)-4-methyl-2-pentenyl, pentadienyl, e.g., 1,3 or 2,4-pentadienyl, and the like.

The term alkynyl include alkyene substituents containing 2 to 6 carbon atoms and may be straight chained as well as branched. It includes such groups as ethynyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynl, 2-pentynyl, 3-methyl-1-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl and the like.

The term cycloalkyl when used alone or in combination is a cycloalkyl group containing from 3 to 18 ring carbon atoms and up to a total of 25 carbon atoms. The cycloalkyl groups may be monocyclic, bicyclic, tricyclic, or polycyclic and the rings are fused. The cycloalkyl may be completely saturated or partially saturated. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl, cyclooctenyl, cycloheptenyl, decalinyl, hydroindanyl, indanyl, fenchyl, pinenyl, adamantyl, and the like. Cycloalkyl includes the cis or trans forms. Furthermore, the substituents may either be in endo or exo positions in the bridged bicyclic systems.

The term "electron-withdrawing and electron donating" refer to the ability of a substituent to withdraw or donate electrons relative to that of hydrogen if the hydrogen atom occupied the same position in the molecule. These terms are well understood by one skilled in the art and are discussed in *Advanced Organic Chemistry*, by J. March, John Wiley and Sons, New York N.Y., pp. 16–18 (1985) and the discussion therein is incorporated herein by reference. Electron withdrawing groups include halo, including bromo, fluoro, chloro, iodo and the like; nitro, carboxy, lower alkenyl, lower alkynyl, formyl, carboxyamido, aryl, quaternary ammonium, trifluoromethyl, aryl lower alkanoyl, carbalkoxy and the like. Electron donating groups include such groups as hydroxy, lower alkoxy, including methoxy, ethoxy and the like; lower alkyl, such as methyl, ethyl, and the like; amino, lower alkylamino, di(loweralkyl)amino, aryloxy such as phenoxy, mercapto, lower alkylthio, lower alkylmercapto, disulfide (lower alkyldithio) and the like. One skilled in the art will appreciate that the aforesaid substituents may have electron donating or electron withdrawing properties under different chemical conditions. Moreover, the present invention contemplates any combination of substituents selected from the above-identified groups.

The term halo includes fluoro, chloro, bromo, iodo and the like.

The term acyl includes lower alkanoyl.

As employed herein, the heterocyclic substituent contains at least one sulfur, nitrogen or oxygen, but also may include one or several of said atoms. The heterocyclic substituents contemplated by the present invention include heteroaromatics and saturated and partially saturated heterocyclic compounds. These heterocyclics may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. They may contain up to 18 ring atoms and up to a total of 17 ring carbon atoms and a total of up to 25 carbon atoms. The heterocyclics are also intended to include the so-called benzoheterocycles. Representative heterocyclics include furyl, thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl, piperazinyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, benzofuryl, benzothienyl, morpholinyl, benzoxazolyl, tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrrolidinyl, furazanyl, N-methylindolyl, methylfuryl, pyridazinyl, pyrimidinyl, pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl, azetidinyl, the N-oxides of the nitrogen containing heterocycles, such as the nitric oxides of pyridyl, pyrazinyl, and pyrimidinyl and the like. The preferred heterocyclic are thienyl, furyl, pyrroly, benzofuryl, benzothienyl, indolyl, methylpyrrolyl, merpholinyl, pyridyl,

pyrazinyl, imidazolyl, pyrimidinyl, pyrazolyl or pyridazinyl. The preferred heterocyclic is a 5 or 6-membered heterocyclic compound. The especially preferred heterocyclic is furyl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, epoxy, pyrimidinyl, or pyridazinyl. The most preferred heterocyclics are furyl, pyrazolyl, pyrrolyl and pyridyl.

The preferred compounds are those wherein n is 1, but di, tri and tetrapeptides are also contemplated to be within the scope of the claims.

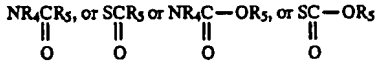
The preferred values of R is aryl lower alkyl, especially benzyl, and the preferred $R_1$ is H or lower alkyl. The most preferred $R_1$ group is methyl.

The most preferred electron donating substituent and electron withdrawing substituent are halo, nitro, alkanoyl, formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(loweralkyl)amino, amine lower alkyl mercapto, mercaptoalkyl, alkylthio; and alkyldithio. The term "sulfide" encompasses mercapto, mercapto alkyl and alkylthio, while the term disulfide encompasses alkyldithio. These preferred substituents may be substituted on any one of $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ or $R_6$, $R_7$ or $R_8$ as defined herein.

The ZY groups representative of $R_2$ and $R_3$ include hydroxy, alkoxy, such as methoxy, ethoxy, aryloxy, such as phenoxy; thioalkoxy, such as thiomethoxy, thioethoxy; thioaryloxy such as thiophenoxy; amino; alkylamino, such as methylamino, ethylamino; arylamino, such as anilino; lower dialkylamino, such as, dimethylamino; trialkyl ammonium salt, hydrazino, alkylhydrazino and arylhydrazino, such as N-methylhydrazino, N-phenylhydrazino, carbalkoxy hydrazino, aralkoxycarbonyl hydrazino, aryloxycarbonyl hydrazino, hydroxylamino, such as N-hydroxylamino (—NH—OH), lower alkoxy amino [$(NHOR_{18})$ wherein $R_{18}$ is lower alkyl], N-lower alkylhydroxyl amino [$(NCR_{18})OH$ wherein $R_{18}$ is lower alkyl], N-lower alkyl-O-lower alkyl hydroxyamino, i.e., [$N(R_{18})OR_{19}$ wherein $R_{18}$ and $R_{19}$ are independently lower alkyl] and o-hydroxylamino (—O—$NH_2$); alkylamido such as acetamido, trifluoroacetamido, lower alkoxyamino, (e.g. $NH(OCH_3)$; and heterocyclicamino, such as pyrazoylamino.

Furthermore, in still another embodiment Z may be O, S, $NR_4$ or $PR_4$ and Y may be hydrogen, lower alkyl or aryl and R, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, n and a are as defined hereinabove.

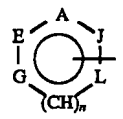
In a still further embodiment, ZY may be



and R, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, n and a are as defined hereinabove.

When $R_2$ or $R_3$ is heterocyclic, the preferred heterocyclics are furyl, tetrahydrofuryl, pyridyl, pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl or epoxy. The most preferred heterocyclic is furyl, pyridyl, pyrazoyl and pyrrolyl.

The preferred heterocyclic groups representative of $R_2$ and $R_3$ have the formula



XI

or those corresponding partially or fully saturated form thereof wherein n is 0 or 1

A, Z, L and J are independently CH, or a heteroatom selected from the group consisting of N, O, S, and

G is CH, or a heteroatom selected from the group consisting of N, O and S,

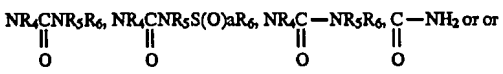
but when n is O, G is CH, or a heterocyclic selected from the group consisting of NH, O and S with the proviso that at most two of A, E, L, J and G are heteroatoms.

If the ring depicted hereinabove contains a nitrogen ring atom, then the N-oxide forms are also contemplated to be within the scope of the invention.

When $R_2$ or $R_3$ is a heterocyclic of the above formula, it may be bonded to the main chain by a ring carbon atom. When n is O, $R_2$ or $R_3$ may additionally be bonded to the main chain by a nitrogen ring atom.

$R_2$ or $R_3$ may independently also be $SO_3^-$, or $SO_2^-$.

Furthermore, ZY may also be



When $R_2$ is alkenyl the alkenyl group is a lower alkenyl group having 1–6 carbon atoms. The alkenyl group may be substituted with an electron donating group and more preferably with an electron withdrawing group, such as COOH.

As indicated hereinabove, Q and A may be O or S; in other words, the main chain may contain only C=O, only —C=S or combinations thereof. All such permutations are contemplated herein. It is preferred that the compounds of the present invention contain no more than 2 C=S moieties, it is even more preferred that the compounds of the present invention contain no more than 1 C=S moiety. The most preferred embodiment are when A and Q are both oxygen.

An embodiment of the present application is one in which the compounds are of Formula I wherein R is lower cycloalkyl or lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group and $R_1$, $R_2$, $R_3$, Z, Y or ZY taken together, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, n and a are as defined herein.

Another embodiment of the present invention include compounds of Formula I wherein $R_1$ is lower cycloalkyl or lower cycloalkyl lower alkyl and $R_1$ may be unsubstituted or substituted with an electron donating group or electron withdrawing group and $R_1$, $R_2$, $R_3$, Z, Y, or ZY taken together, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ n and a are as defined hereinabove.

Another embodiment of the present invention includes compounds of Formula I wherein $R_2$ is lower cycloalkyl or lower cycloalkyl lower alkyl and $R_2$ may be unsubstituted or substituted with an electron donating group or electron withdrawing group, and R, $R_1$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$ and a are as defined hereinabove.

Still another embodiment of the present invention include compounds of Formula I wherein $R_3$ is lower cycloalkyl or lower cycloalkyl lower alkyl and $R_3$ may be unsubstituted or substituted with an electron donating or electron withdraw-

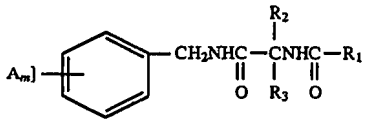
ing group and R, $R_1$, $R_2$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, n and a are as defined hereinabove.

A further embodiment of the present invention include compounds of Formula I wherein Z is $S(O)_a$ and R, $R_1$, $R_2$, $R_3$, Y, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, n and a are as defined herein.

It is preferred that one of $R_2$ and $R_3$ is hydrogen.

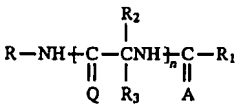
In a preferred embodiment, one of $R_2$ and $R_3$ is hydrogen and that the other is heterocyclic. It is preferred that one of $R_2$ and $R_3$ is a heterocyclic having Formula XI. The preferred heterocyclics include furyl, thienyl, benzothienyl, benzofuryl, oxazolyl, thiazolyl, isoxazolyl, indolyl, pyrazolyl, isoxazolidinyl, benzothienyl, benzofuryl, morpholinyl, indolyl, pyrrolyl, furfuryl, and methylpyrrolyl, pyridyl, pyrazinyl, imidazolyl, pyrimidinyl or pyridazinyl, pyrazolyl, or epoxy. In another preferred embodiment, one of $R_2$ and $R_3$ is alkyl (e.g. methylisopropyl), aryl (e.g., phenyl), 2-thiomethylethyl, lower alkoxy (e.g., ethoxy, methoxy), anilino, propenyl, alkylamino (e.g., ethylamino or methylamino). In another preferred embodiment, one of $R_2$ and $R_3$ is hydrogen and the other is heterocyclic lower alkyl, lower alkenyl, amino, lower alkoxy amino, N-lower alkylhydroxyamino, lower alkoxyamino, N-lower alkyl-O-lower alkylhydroxyamino or aralkoxycarbonylhydrazino.

Preferred compounds of the present invention have the following general formula:



wherein $R_1$ is H or lower alkyl, $R_2$ and $R_3$ are as defined above and A is hydrogen or an electron donating group or electron-withdrawing group and m is 0–5. It is preferred that A is hydrogen (i.e., m=0). However, values of m equalling 1, 2 or 3 are also preferred.

Preferred embodiments include compounds of Formula I



(I)

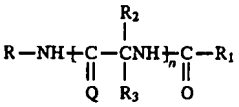
wherein

R and $R_1$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, each unsubstituted or substituted with at least one substituent;

$R_2$ and $R_3$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, each unsubstituted or substituted with at least one substituent; halogen or a heteroatom containing oxygen, nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted; and

n is 1 to 4.

Another preferred embodiment is a compound having Formula I



(I)

wherein

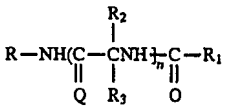
R is aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

$R_1$ is H or lower alkyl, unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

$R_2$ and $R_3$, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron donating substituent, halogen or a heteroatom containing oxygen, nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted; and

n is 1 to 4.

Another preferred embodiment of the present invention is a compound of Formula I



wherein

R is aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each of which may be unsubstituted or substituted with at least one halo, nitro, acyl, carboxyl, carboalkoxy, carboxamide, cyano, sulfonyl, sulfoxide (sulfinyl), heterocyclic, guanidine, quaternary ammonium hydroxy, alkoxy, alkyl, amino, phenoxy, mercapto, sulfide or disulfide;

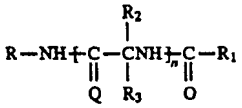
$R_1$ is H or lower alkyl which may be unsubstituted or substituted with at least one halo, nitro, acyl, carboxamide, cyano, sulfonyl, sulfoxide (sulfinyl), heterocyclic, guanidine, quaternary ammonium, hydroxy, lower alkoxy, amino, phenoxy, sulfide, or disulfide;

$R_2$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent; halogen or a heteroatom consisting of oxygen, nitrogen, sulfur or phosphorous, said heteroatom being substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted;

$R_3$ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent; halogen or a heteroatom consisting of oxygen, nitrogen, sulfur, or phosphorous said heteroatom being substituted with hydrogen, lower alkyl or aryl, said lower alkyl of aryl groups being substituted or unsubstituted;

and n is 1 to 4;

Another preferred embodiment is a compound of Formula I



(I)

wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group;

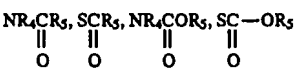
$R_1$ is hydrogen or lower alkyl, unsubstituted or substituted with an electron donating group or an electron withdrawing group and

$R_2$ and $R_3$ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, or Z—Y wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, $S,S(O)_a$, $NR_4$, $PR_4$ or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, or halo and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is $NR_4NR_5R_7$, $NR_4OR_5$, $ONR_4R_7$, $OPR_4R_5$, $PR_4OR_5$, $SNR_4R_7$, $NR_4SR_7$, $SPR_4R_5$ or $PR_4SR_7$, $NR_4PR_5R_6$ or $PR_4NR_5R_7$,



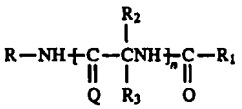
$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

$R_7$ is $R_6$ or $COOR_8$ or $COR_8$, $R_8$ is hydrogen or lower alkyl, or aryl lower alkyl, wherein the aryl or lower alkyl groups may be unsubstituted or substituted with an electron withdrawing or electron donating group,

n is 1–4 and

a is 1–3.

Another class of preferred compounds of the Formula I have the formula



wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic alkyl which is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;

$R_1$ is hydrogen or lower alkyl which is unsubstituted or substituted with at least one electron withdrawing group or one electron donating group,

$R_2$ and $R_3$ are independently hydrogen, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, Z—Y or a heterocyclic group which may be unsubstituted or substituted with at least one electron withdrawing or one electron donating group, with the proviso that $R^2$ and $R^3$ cannot both be hydrogen;

Z is O, S, $NR_4$, $PR_4$ or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl or halo, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond; or

ZY taken together is $NR_4NR_5R_6$, $NR_4OR_5$, $ONR_4R_5$, $OPR_4R_5$, $PR_4OR_5$, $SNR_4R_5$, $NR_4SR_5$, $SPR_4R_5$, or $PR_4SR_5$, $NR_4PR_5R_6$ or $PR_4NR_5R_6$,

$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

n is 1–4.

Of this preferred group, it is especially preferred that n is 1.

The preferred compounds are those in which R is aryl, aryl lower alkyl, heterocyclic, or heterocyclic lower alkyl, $R_1$ is hydrogen or lower alkyl, $R_2$ and $R_3$ are independently hydrogen, heterocyclic, lower alkyl, aryl, lower alkoxy, lower alkenyl, amino, hydroxylamino, lower alkoxy amino, N-lower alkyl hydroxyamino, N-lower alkyl-o-lower alkyl hydroxyamino, aralkoxy carbonyl hydrazino or alkylmercapto and n is 1.

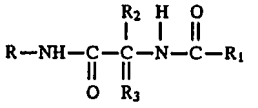
In another preferred embodiment, n is 1, R and $R_1$ are as defined hereinabove and one of $R_2$ and $R_3$ is hydrogen and the other is heterocyclic, heterocyclic lower alkyl, aryl N-hydroxylamino, lower alkoxyamino, N-lower alkylhydroxylamino, N-lower alkyl-O-lower alkylhydroxyamino.

Another preferred embodiment is wherein n is 1, R and $R_1$ are as defined hereinabove, one of $R_2$ and $R_3$ is as defined hereinabove or the other is heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, aryl, N-hydroxylamino, lower alkoxy amino, N-lower alkyl hydroxylamino, N-lower alkyl-o-lower alkyl hydroxylamino, lower alkoxy, dialkyl lower amino, lower alkylamino, aryl lower alkyloxy hydrazino, or lower alkylmercapto.

The various combination and permutations of the Markush groups of $R_1$, $R_2$, $R_3$ R and n described herein are contemplated to be within the scope of the present invention. Moreover, the present invention also encompasses compounds and compositions which contain one or more elements of each of the Markush groupings in $R_1$, $R_2$, $R_3$, n and R and the various combinations thereof. Thus, for example, the present invention contemplates that $R_1$ may be one or more of the substituents listed hereinabove in combination with any and all of the substituents of $R_2$, $R_3$ and R with respect to each value of n.

The compounds of the present invention may contain one (1) or more asymmetric carbons and may exist in racemic and optically active forms. The configuration around each asymmetric carbon can be in either the D or L form. (It is well known in the art that the configuration around a chiral carbon atoms can also be described as R or S in the Cahn-Prelog-Ingold nomenclature system). All of the various configurations around each asymmetric carbon, including the various enantiomers and diastereomers as well as racemic mixtures and mixtures of enantiomers, diastereomers or both are contemplated by the present invention.

In the principal chain, there exists asymmetry at the carbon atoms to which the groups $R_2$ and $R_3$ are attached as substituted. When n is 1, the compounds of the present invention is of the formula



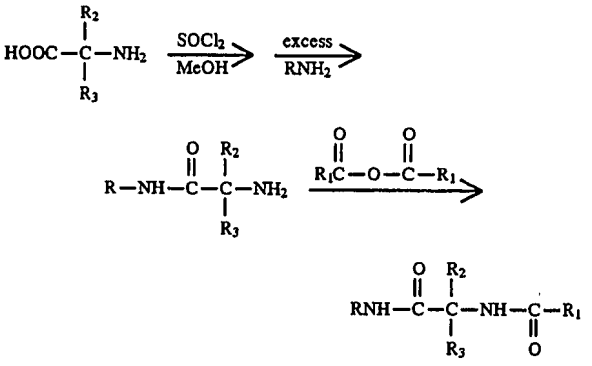
wherein R, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, Z and Y are as defined previously. As used herein, the term configuration shall refer to the configuration around the carbon atom to which $R_2$ and $R_3$ are attached, even though other chiral centers may be present in the molecule. Therefore, when referring to a particular configuration, such as D or L, it is to be understood to mean the stereoisomer, including all possible enantiomers and diastereomers. The compounds of the present invention are directed to all of the optical isomers, i.e., the compounds of the present invention are either the L-stereoisomer or the D-stereoisomer. These stereoisomers may be found in mixtures of the L and D stereoisomer, e.g., racemic mixtures. The D stereoisomer is preferred.

Depending upon the substituents, the present compounds may form addition salts as well. All of these forms are contemplated to be within the scope of this invention including mixtures of the stereoisomeric forms.

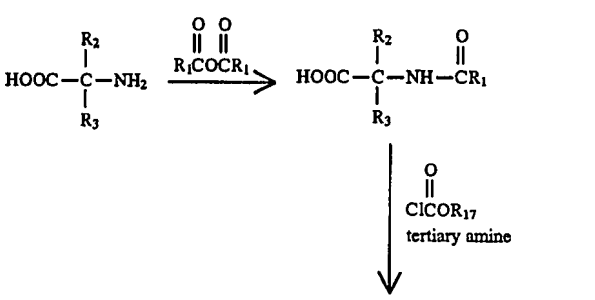
The following three schemes of preparation are generally exemplary of the process which can be employed for the preparation of the present complex. Although the compounds in the schemes hereinabove contain only the

moiety, it is just as applicable to compounds of Formula I wherein either A or Q is sulfur or both A or Q are sulfur.

Scheme I



Scheme II



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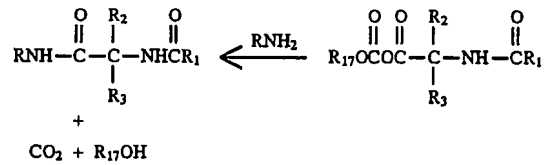
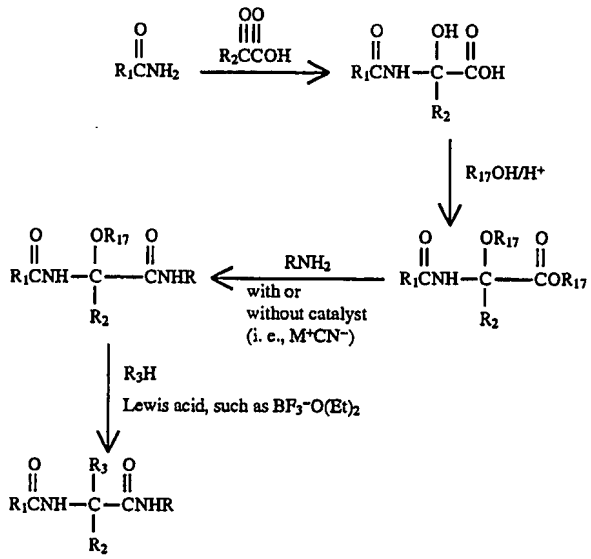
Scheme II



wherein

$R_{17}$=lower alkyl, aryl, aryl lower alkyl.

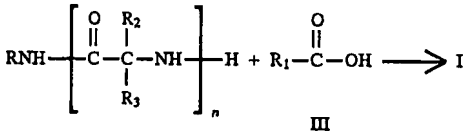
Scheme III



wherein

$R_3$=aryl, heteroaromatic and $R_{17}$ is as defined hereinabove.

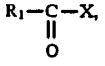
More specificically these compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. For instance, compounds of Formula I can be prepared by reacting amines of Formula II with an acylating derivative of a carboxylic acid of Formula III under amide forming conditions:



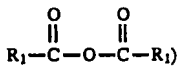
II III

wherein R, $R_1$, $R_2$, $R_3$ and are as defined hereinabove and n=1.

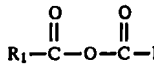
The amide forming conditions referred to herein involve the use of known derivatives of the described acids, such as the acyl halides, (e.g.,



wherein X is Cl, Br and the like), anhydrides (e.g.,



mixed anhydrides, lower alkyl esters, carbodiimides, carbonyldiimidazoles, and the like. It is preferred that the acylating derivative used is the anhydride,

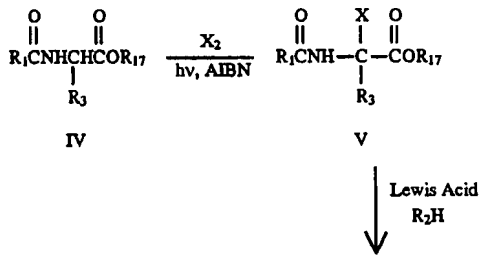


When alkyl esters are employed, amide bond formation can be catalyzed by metal cyanides such as sodium or potassium cyanides.

Another exemplary procedure for preparing compounds wherein at least one of $R_2$ and $R_3$ is aromatic or heteroaromatic is depicted in Scheme IV.

The ester (IV) is reacted with halogen and ultraviolet light in the presence of a catalyst, e.g., AIBN, to form the halo derivative (V). (V) is reacted in the presence of a Lewis acid, such as zinc chloride, with an aromatic or heteroaromatic compound to form the compound (VI). (VI) in turn is hydrolyzed and then reacted with alkylhaloformate, such as alkylchloroformate in the presence of a tertiary amine to generate the mixed N-acyl amino acid carbonic ester anhydride (VIII). This intermediate is reacted with an amine under amide forming conditions to give the compound of Formula I. Alternatively, (VI) can be reacted directly with an amine ($RNH_2$) optionally in the presence of a metal catalyst, such as metal cyanides, e.g., potassium or sodium cyanide, under amide forming conditions to form a compound of Formula I. Alternatively, compound VIII can be prepared by an independent method and converted to VI which is then reacted with an amine, with or without catalyst to form the compound of Formula I.

Scheme IV



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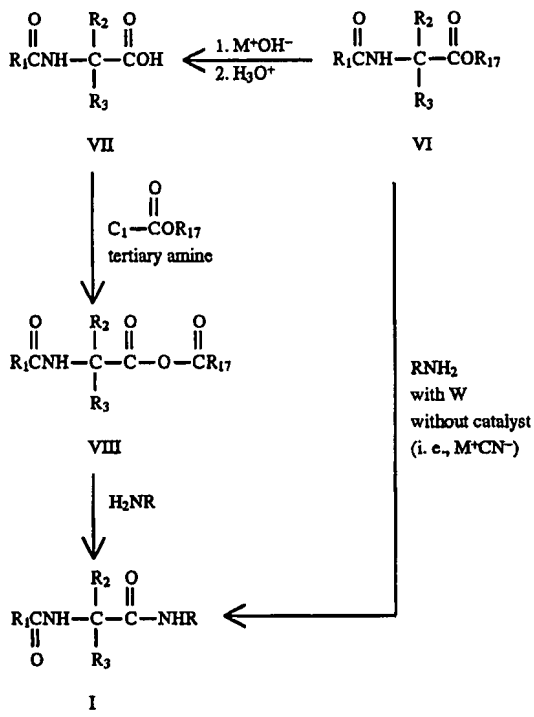
Scheme IV



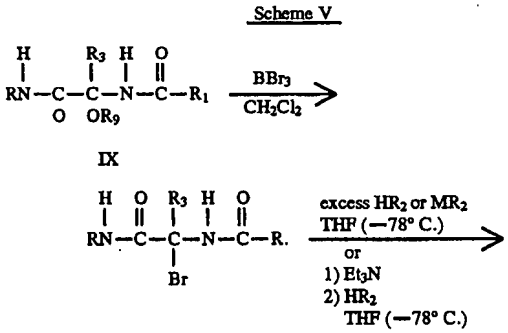
X=halogen (i.e., Cl, Br)

$R_{17}$=lower alkyl, aryl, arly lower alkyl

M+=metal cation (i.e., $Na^+$, $K^+$)

Two additional synthetic routes may be employed for the preparation of compounds wherein $R_2$ or $R_3$ is Z—Y as defined hereinabove. In one scheme, for the preparation of these complexes, a substitution reaction is used:

Scheme V



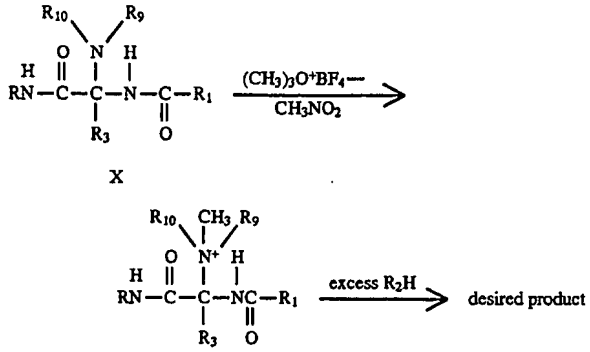
In the above scheme, $R_9$ is lower alkyl, $R_2$ is Z—Y and Z, Y, R, $R_3$ and $R_1$ are as defined hereinabove.

The ether functionality on IX can be cleaved by treatment with Lewis acids, such as $BBr_3$ in an inert solvent such as methylene chloride to form the corresponding halo (bromo) derivative. Addition of either an excess of the H—$R_2$ or $MR_2$ or the sequential addition of triethylamine and H—$R_2$ to a THF mixture containing the halo derivative furnishes the desired product. For example, in the case wherein the

compound of Formula IX is 2-acetamido-N-benzyl-2-ethoxy acetamide, its treatment with $BBr_3$ in $CH_2Cl_2$ led to the formation of the α-bromo derivative, 2-acetamido-N-benzyl-2-bromoacetamide. Addition of an excess of $HR_2$ or the sequential addition of $HR_2$ to a THF mixture containing the bromo adduct furnishes the desired product.

In another procedure, the product wherein $R_2$ or $R_3$ is Z—Y can also be prepared by substitution reaction on a quaternary ammonium derivative of the compound of Formula I as outlined below

Scheme VI




In scheme VI, R, $R_1$, $R_3$ and R are as defined hereinabove, $R_2$ is Z—Y and $R_9$ and $R_{10}$ are independently lower alkyl. In scheme VI, methylation of compound X with a methylation reagent, such as trimethyloxonium tetrafluoroborate provided the corresponding ammonium derivative. Subsequent treatment of the ammonium salt with $HR_2$ furnishes the desired product. For example, methylation of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide with trimethyloxonium tetrafluoroborate in nitromethane furnished the quaternary ammonium derivative, 2-acetamido-N-benzyl-(N,N,N-trimethylammonium) acetamide tetrafluoroborate in high yields. Subsequent treatment of the salt with the $HR_2$ reagent in the methanol leads to the production of the desired product.

As in any organic reaction, solvents can be employed such as methanol, ethanol, propanol, acetone, tetrahydrofuran, dioxane, dimethylformamide, dichloromethane, chloroform, and the like. The reaction is normally effected at or near room temperature, although temperatures from 0° C. up to the reflux temperature of the reaction mixture can be employed.

As a further convenience, the amide forming reaction can be effected in the presence of a base, such as tertiary organic amine, e.g., triethylamine, pyridine, 4-methylmorpholine, picolines and the like, particularly where hydrogen halide is formed by the amide forming reaction, e.g., the reaction acyl halide and the amine of Formula II. Of course, in those reactions where hydrogen halide is produced, any of the commonly used hydrogen halide acceptors can also be used.

The exact mineral acid or Lewis acid employed in the reaction will vary depending on the given transformation, the temperature required for the conversion and the sensitivity of the reagent toward the acid in the reaction employed.

Compounds of the present invention in which Q or A is S are prepared from the corresponding compounds in which Q or A is O by art recognized techniques. For example, one reagent that can be used is Lawesson's reagent, i.e., [2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2-,4-disulfide]. This reagent is a known reagent for the thiation of such compounds as ketones, carboxamides, esters, lactones, lactams, imides, enamines, and S-substituted thioesters. Thus, this reagent can be used to transform compounds of Formula I wherein Q or A is O to compounds wherein one or both of Q or A is S. The number of



groups in the final product is dependent upon the amount of reagent added and the number of



groups present (i.e., the value of n) in the reactants having Formula I. For example, if n is 1, and both Q and A are oxygen, than the compounds of Formula I have two



groups. Thus, if it is desired that both



groups be transformed to



then approximately equimolar amount or a slight excess of is added to compounds of Formula I. On the other hand, if only one



group is desired in the final product, then approximately ½ molar equivalent of Lawesson's reagent is used.

Furthermore, it is not necessary to add the reagent at the last step of the synthesis; the reagent can be added at any stage of the syntheses outlined in Schemes I–VI hereinabove. As before, the amount of the reagent added depends upon the number of



desired in the product, and the number of



groups in the reactant.

Regardless of which step in the synthesis the reagent is added, the reagent and the compound of Formula I having at least one

group or an intermediate thereof is dissolved in an inert solvent, such as THF and heated at a temperature effective to convert the



group to



Temperatures ranging from room temperature to the reflux temperature of the solvent can be used. In cases when n=1, it is preferred that the reaction is heated to about reflux if both Q and A are converted to S and that about room temperature be used if one of Q or A is converted to S.

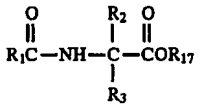
The various substituents on the present new compounds, e.g., as defined in R, $R_1$, $R_2$ and $R_3$ can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by the known methods of substitution or conversion reactions. For example, the nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Alkanoyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups can be then transformed to the corresponding alkyl groups by various methods, including the Woff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono, dialkylamino and trialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding thioethers or ethers, respectively. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

In the above reactions, if the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis," by T. W. Greene, John Wiley & Sons, 1981.

Resulting mixtures of isomers can be separated in the pure isomers by methods known to one skilled in the art, e.g., by fractional distillation, crystallization and/or chromotagraphy.

The present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers, which can be resolved. Optically pure functionalized amino acid derivatives can be prepared directly from the corresponding pure chiral intermediate. Racemic products can likewise be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g., by fractional crystallization, by selective enzymatic hydrolysis, e.g., papain digestion, or by use of a chiral stationary phase in chromotagraphy (HPLC). For a discussion of chiral stationary phases for HPLC, See, DeCamp, *Chirality*, 1, 2–6 (1989), which is incorporated herein by reference with the same force and effect as if fully set forth herein.

For example, a racemic mixture of any of the intermediate in any of the schemes, e.g.,



wherein $R_{17}$ is H (which can be prepared according to the procedures of Schemes 1, 2, 3 or 4) is reacted with an optically active amine, $RNH_2$, e.g., (R)(+)α-methylbenzylamine to form a pair of diasteroomeric salts. Diastereomers can then be separated by recognized techniques known in the art, such as fractional recrystallization and the like.

In another method, a racemic mixture of final products or intermediates can be resolved by using enzymatic methods. Since enzymes are chiral molecules, it can be used to separate the racemic modification, since it will preferentially act on one of the compounds, without affecting the enantiomer. For example, acylase, such as acylase I, can be used to separate the racemic modification of an intermediate D,L(±)α-acetamido-2-furanacetic acid. It acts on the L (±)α-acetamido-2-furanacetic acid, but will not act on the D enantiomer. In this way, the D(−)α-acetamido-2-furanacetic acid can be isolated. The intermediate can then react with the amine ($RNH_2$) under amide forming conditions as described hereinabove to form the compound of Formula I.

The active ingredients of the therapeutic compositions and the compounds of the present invention exhibit excellent anticonvulsant activity when administered in amounts ranging from about 10 mg to about 100 mg per kilogram of body weight per day. A preferred dosage regimen for optimum results would be from about 20 mg to about 50 mg per kilogram of body weight per day, and such dosage units are employed that a total of from about 1.0 gram to about 3.0 grams of the active compound for a subject of about 70 kg of body weight are administered in a 24-hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response and is preferably administered one to three times a day in dosages of about 600 mg per administration. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that the active compound may be administered in an convenient manner such as by the oral, intraveneous (where water soluble), intramuscular or subcutaneous routes.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 1000 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintergrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin.

The active compound may also be administered parenterally or intraperitoncally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin; by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 5 to about 1000 mg, with from about 250 to about 750 mg being preferred. Expressed in proportions, the active compound is generally present in from about 10 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

The compounds of the present invention may be administered in combination with other anti-convulsant agents, such as phenytoin, phenbarbitol, mephenytoin, and phenacemide, and the like. This combination is likely to exhibit synergistic effects.

For a better understanding of the present invention together with other and further objects, reference is made to the following description and examples.

General Methods.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR-4250 and Perkin-Elmer 1330 and 283 spectrophotometers and calibrated against the 1601-$cm^{-1}$ band of polysytrene. Absorption values are expressed in wavenumbers ($cm^{-1}$). Proton nuclear magnetic resonance ($^1H$ NMR) spectra were recorded on Varian Associates Models T-60 and FT-80A, General Electric QE 300, and Nicolet NT-300 NMR spectrometers. Carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra were run on a Varian Associates Models FT-80A General Electric QE 300 and Nicolet NT-300 instrument. Chemical shifts are in parts per million ($\delta$ values) relative to $Me_4Si$, and coupling constants (J values) are in hertz. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-

Packard 5930 gas chromotagraph-mass spectrometer and a Bell-Howell 21–491 spectrometer as well as at the Eli Lilly Laboratories on a Varian MAT-CH-5 spectrometer. High-resolution (EI mode) mass spectra were performed by Drs. James Hudson and John Chinn at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, Mich. and at the Eli Lilly Research Laboratories.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All anhydrous reactions were run under nitrogen, and all glassware was dried before use. In particular, acetonitrile and triethylamine were distilled from $CaH_2$, while dichloromethane was distilled from $P_2O_5$. Acetic anhydride, benzaldehyde and ethyl chloroformate were fractionally distilled.

Preparation of N-Acetyl-D- and L-amino acid-N-benzylamides.

General Procedure.

The D- or L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane. The following examples 1–7 were prepared according to this procedure.

## EXAMPLE 1

Preparation of N-Acetyl-D,L-alanine-N'-benzylamide.

Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a methylene chloride solution (30 mL) of D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to stir at room temperature (3 h). The mixture was then successively washed with $H_2O$ (15 mL), 1% aqueous NaOH (15 mL) and $H_2O$ (15 mL), dried ($Na_2SO_4$) and concentrated in vacuo. The residue was recrystallized from $CH_2Cl_2$.

Yield: 2.50 g (54%).

mp 139°–141° C.

$^1$H NMR (DMSO-$d_6$): δ 1.22 (d,J=7.1 Hz, 3H), 1.84 (s, 3H), 4.04–4.50 (m, 3H), 7.26 (s, 5H), 8.11 (br d,J=7.3 Hz, 1H), 8.42 (br t,J=6 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1, 139.4, 168.9, 172.4 ppm.

IR ($CHCl_3$) 3440, 3300, 3005, 1660, 1515 cm$^{-1}$.

Mass spectrum (CI mode), m/e: 221 (P+1); mol wt 220.1208 (Calculated for $C_{12}H_{16}N_2O_2$, 220.1212).

## EXAMPLE 2

N-Acetyl-D-alanine-N'-benzylamide.

Yield: 1.36 g (56%).

mp 139°–141° C.

$[\alpha]_D^{23}$=+36.2 (c 2.5, MeOH).

$^1$H NMR (80 MHz, DMSO-$d_6$): δ 1.25 (d,J=7.1 Hz, 3H), 1.86 (s, 3H), 4.10–4.50 (m, 1H), 4.30 (d,J=6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d,J=7.3 Hz, 1H), 8.40 (t,J=6.0 Hz, 1H).

$^{13}$C NMR (80 MHz, DMSO-$d_6$): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

Elemental analysis Calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.31% C; 7.28% H; 12.63% N.

## EXAMPLE 3

N-Acetyl-L-alanine-N'-benzylamide.

Yield: 1.11 g (46%).

mp 139°–142° C.

$[\alpha]_d^{23}$ =–35.3 (c 2.5, MeOH).

$^1$H NMR (80 MHz, DMSO-$d_6$): δ 1.23 (d,J=7.2 Hz, 3H), 1.86 (s, 3H), 4.26–4.35 (m, 1H), 4.29 (d,J=5.8 Hz, 2H), 7.22–7.33 (s, 5H), 8.10 (d,J=7.4 Hz, 1H), 8.42 (t,J=5.8 Hz, 1H).

$^{13}$C NMR (80 MHz, DMSO-$d_6$): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C), 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

Elemental analysis Calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.58% C; 7.32% H; 12.43% N.

## EXAMPLE 4

Preparation of N-Acetyl-D,L-phenylglycine-N'-methylamide.

Acetic anhydride (2.90 g, 28 mmol) was added dropwise to D,L-phenylglycine-N-methylamide (3.4 g, 20 mmol) and allowed to stir at room temperature (1.5 h). During this time, a copious white precipitate formed. This material was collected by filtration, dried in vacuo and recrystallized from absolute alcohol.

Yield: 2.00 g (49%).

mp 232°–235° C. (dec).

$^1$H NMR (DMSO-$d_6$): δ 1.89 (s, 3H), 2.58 (d,J=4.6 Hz, 3H), 5.42 (d,J=8.1 Hz, 1H), 7.35 (s, 5H), 8.18 (br q,J=4.2 Hz, 1H), 8.47 (d,J=8.1 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 22.4, 25.5, 56.3, 127.1, 127.3, 128.1, 139.0, 168.9, 170.3 ppm.

IR (KBr): 3310, 1645 cm$^{-1}$.

Mass spectrum (CI mode), m/e: 207 (P+1).

Elemental analysis Calculated for $C_{11}H_{14}N_2O_2$ 64.06% C; 6.86% H; 13.58% N. Found 63.79% C; 6.66% H; 13.27% N.

## EXAMPLE 5

Preparation of N-Acetylglycine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4–6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 1.84 g (81%).

mp 140°–142° C.

$^1$H NMR (DMSO-$d_6$): δ 1.88 (s, 3H), 3.74 (d,J=5.3 Hz, 2H), 4.30 (d,J=5.1 Hz, 2H), 7.27 (s, 5H), 8.37 (br s, 1H), 8.75 (br s, 1H).

$^{13}$C NMR (DMSO-$d_6$): 22.5, 42.0, 42.5, 126.6, 127.1 (2C), 128.1 (2C), 139.3, 169.0, 169.6 ppm.

IR (KBr): 3060, 1655, 1640, 1560, 1545, 1450, 1300, 740, 710 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 206 (3), 147 (12), 106 (100), 91 (75), 73 (50).

Elemental analysis Calculated for $C_{11}H_{14}N_2O_2$ 64.05% C; 6.86% H; 13.58% N. Found 64.03% C; 6.79% H; 13.61% N.

EXAMPLE 6

Preparation of N-Acetyl-D,L-valine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4–6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.35 g (86%).

mp 192°–193° C.

$^1$H NMR (DMSO-$d_6$): δ 0.83 (d,J=6.7 Hz, 6H), 1.87 (s, 3H), 1.73–2.09 (m, 1H), 4.11 (d,J=8.8 Hz, 1H), 4.27 (d,J=5.8 Hz, 2H), 7.26 (s, 5H), 7.89 (d,J=8.8 Hz, 1H), 8.84 (t,J=5.8 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 18.1, 19.2, 22.4, 30.2, 41.9, 57.8, 126.6, 127.1 (2C), 128.1 (2C), 139.4, 169.2, 171.1 ppm.

IR (KBr): 1625, 1540, 1535, 1450, 1380, 1290, 750, 695 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 142 (16), 114 (43), 106 (29), 91 (57), 72 (100).

Elemental analysis Calculated for $C_{14}H_{20}N_2O_2$ 67.70% C; 8.13% H; 11.28% N. Found 67.58% C; 8.05% H; 11.10% N.

EXAMPLE 7

Preparation of N-Acetyl-D,L-phenylglycine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4–6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.05 g (66%).

mp 202°–203° C.

$^1$H NMR (DMSO-$d_6$): δ 1.91 (s, 3H), 4.27 (d,J=5.6 Hz, 2H), 5.50 (d,J=7.9 Hz, 1H), 7.21 (s, 5H), 7.36 (s, 5H), 8.38–8.86 (m, 2H).

$^{13}$C NMR (DMSO-$d_6$): 22.3, 42.0, 56.3, 126.6 (2C), 127.0, 127.1 (2C), 127.4 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 169.9 ppm.

IR (KBr): 3020, 1635, 1580, 1540, 1450, 1265, 745, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 283 (20), 264 (21), 149 (100), 131 (20), 118 (34), 106 (92), 91 (70), 79 (56), 77 (54), 65 (45), 51 (37).

Elemental analysis Calculated for $C_{17}H_{18}N_2O_2$ 72.31% C; 6.44% H; 9.92% N. Found 72.49% C; 6.47% H; 9.89% N.

Preparation of N-Acetyl-D- and L-phenylglycine-N-benzylamide.

General Procedure.

The chiral Boc-protected phenylglycine-N-benzylamide was dissolved in trifluoroacetic acid (0.04M) and was stirred at room temperature (30 min), during which time gas evolved. The solution was concentrated in vacuo and the residue was redissolved in enough methanol to form a solution of 0.2M. Methanesulfonic acid (1 equiv) was added dropwise and stirred for 5 min. After concentrating the solution in vacuo, the residue was repeatedly dissolved in methanol and the solvent was removed (3 times). The residue was then dried under vacuum (18 h), leaving a yellow oil.

Without further purification, the phenylglycine-N-benzylamide methanesulfonate was dissolved in tetrahydrofuran (0.2M) and then was cooled in an ice bath. Triethylamine (2 equiv) was added dropwise, followed by acetyl chloride (1 equiv). The ice bath was removed and stirring was continued at room temperature (18 h). The solution was concentrated in vacuo and the residue was recrystallized from 1:1 95% ethanol/water. Examples 8 and 9 were prepared according to this procedure.

EXAMPLE 8

N-Acetyl-D-phenylglycine-N-benzylamide.

The reaction was run on an 11.9 mmol scale.

Yield: 2.97 g (88%).

mp 219°–221° C.

$[\alpha]_D$=–103.0 (c 1%, EtOH).

$^1$H NMR (DMSO-$d_6$): δ 1.91 (s, 3H), 4.27 (d,J=5.5 Hz, 2H), 5.50 (d,J=7.8 Hz, 1H), 7.14–7.44 (m, 10H), 8.56 (d,J=7.8 Hz, 1H), 8.79 (t,J=5.5 Hz, 1H).

$^{13}$C NMR (DMSO-$_6$): 22.4, 42.0, 56.4, 126.7, 127.0 (2C) 127.2 (2C), 127.4, 127.9 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 170.0 ppm.

IR (KBr): 3260, 1620, 1525, 1450, 1370, 720, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 203 (2), 149 (94), 106 (100), 91 (32), 86 (43), 77 (14).

Elemental analysis Calculated for $C_{17}H_{18}N_2O_2$ 72.32% C; 6.43% H; 9.92% N. Found 72.04% C; 6.22% H; 9.78% N.

EXAMPLE 9

N-Acetyl-L-phenylglycine-N-benzylamide.

Beginning with 16.1 mmol N-t-Boc-L-phenylglycine-N-benzylamide.

Yield: 2.99 g (66%).

mp 221°–222° C.

$[\alpha]_D$=+105.1 (c 1%, EtOH).

$^1$H NMR (DMSO-$d_6$): δ 1.99 (s, 3H), 4.36 (d,J=5.6 Hz, 2H), 5.60 (d,J=8.0 Hz, 1H), 7.23–7.53 (m, 10H), 8.60 (d,J=8.0 Hz, 1H), 8.83 (t,J=5.6 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 22.4, 42.1, 56.5, 126.8, 127.1 (2C), 127.3 (2C), 127.5, 128.2 (4C), 139.0, 139.1, 169.1, 170.1 ppm.

IR (KBr): 3295, 1630, 1530, 1450, 1395, 720, 695 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 223 (1), 203 (2), 149 (98), 106 (100), 91 (32), 86 (43), 77 (11).

Elemental analysis Calculated for $C_{17}H_{18}N_2O_2$ 72.32% C; 6.43% H; 9.92% N. Found 72.53% C; 6.49% H; 9.67% N.

EXAMPLE 10

Preparation of N-Acetyl-D,L-alanine-N-(3-methoxy) benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4–6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 0.47 g (17%).

mp 112°–115° C.

$^1$H NMR (DMSO-$d_6$): δ 1.23 (d,J=7.1 Hz, 3H), 1.85 (s, 3H),

3.73 (s, 3H), 3.99–4.48 (m, 1H), 4.25 (d,J=6.1 Hz, 2H), 6.58–7.35 (m, 4H), 8.05 (d,J=7.4 Hz, 1H), 8.35 (t,J=6.0 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 18.1, 22.5, 41.8, 48.3, 54.9, 112.2, 112.3, 119.0, 129.2, 141.0, 159.3, 169.0, 172.4 ppm.

IR (KBr): 3270, 3065, 1625, 1580, 1450, 1260, 1150, 1095, 900, 775, 700, 690 cm$^{-1}$.

Elemental analysis Calculated for $C_{13}H_{18}N_2O_3$ 62.37% C; 7.26% H; 11.19% N. Found 62.29% C; 7.13% H; 11.08% N.

## EXAMPLE 11

Preparation of N-Trimethylacetyl-D,L-alanine-N-benzylamide.

D,L-Alanine-N-benzylamide (3.56 g, 20 mmol) was dissolved in dichloromethane (25 mL) and trimethylacetic anhydride (4.10 g, 4.46 mL, 22 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The solid residue was recrystallized from benzene/petroleum ether (30°–60° C.).

Yield: 2.07 g (40%).

mp 123°–124° C.

$^1$H NMR (DMSO-$d_6$): δ 1.12 (s, 9H), 1.27 (d,J=7.1 Hz, 3H), 4.23–4.42 (m, 1H), 4.31 (d,J=5.4 Hz, 2H), 7.23–7.30 (m, 5H), 7.38 (d,J=7.4 Hz, 1H), 8.26 (t,J=5.4 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 18.1, 27.2 (3C), 37.9, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 172.5, 177.1 ppm.

IR (KBr): 3300, 1630, 1535 (br), 1455, 745, 695 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 262 (2), 203 (19), 156 (18), 128 (51), 106 (31), 91 (100), 77 (15), 65 (28).

Elemental analysis Calculated for $C_{15}H_{22}N_2O_2$ 68.66% C; 8.47% H; 10.68% N. Found 68.91% C; 8.14% H; 10.61% N.

## EXAMPLE 12

Preparation of N-Acetyl-D,L-methionine-N-benzylamide.

N-Acetyl-D,L-methionine (4.78 g, 25 mmol) was combined with acetonitrile (75 mL) and the mixture was placed into an ice/salt water bath (−5° C.). Triethylamine (2.53 g, 3.48 mL, 25 mmol,) was added dropwise, followed by ethyl chloroformate (2.71 g, 2.39 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0° C. The mixture was then stirred at −5° C. (20 min). Benzylamine (3.00 g, 3.06 mL, 28 mmol) in acetonitrile (5 mL) was added dropwise and the mixture was stirred at −5° C. (1 h) and then room temperature (18 h).

The mixture was filtered and a white precipitate was collected and dried in vacuo and identified as the desired product ($^1$H NMR and $^{13}$C NMR analyses). The filtrate was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride.

The latter filtrate containing tetrahydrofuran was concentrated in vacuo and the resulting residue was purified by flash column chromatography (ethyl acetate). A white solid ($R_f$=0.50, ethyl acetate) was isolated and was identified as the desired product ($^1$H NMR and $^{13}$C NMR analyses). The two solids identified as N-acetyl-D,L-methionine-N-benzylamide were combined and recrystallized from benzene/petroleum ether (30°–60° C.).

Yield: 2.98 g (43%).

mp 134°–135° C.

$^1$H NMR (DMSO-$d_6$): δ 1.69–1.94 (m, 2H), 1.87 (s, 3H), 2.02 (s, 3H), 2.29–2.59 (m, 2H), 4.10–4.53 (m, 1H), 4.29 (d,J=6.0 Hz, 2H), 7.26 (s, 5H), 8.12 (d,J=8.5 Hz, 1H), 8.47 (t,J=6.0 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 14.6, 22.5, 29.7, 31.8, 42.0, 52.0, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.5, 171.4 ppm.

IR (KBr): 3280, 1630, 1545, 1460, 750, 700 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 280 (3), 206 (100), 164 (29), 146 (20), 106 (54), 91 (76), 77 (14), 65 (24).

Elemental analysis Calculated for $C_{14}H_{20}N_2O_2S$ 59.96% C; 7.20% H; 9.99% N. Found 60.02% C; 7.14% H; 9.91% N.

## EXAMPLE 13

Preparation of N-Acetylalanine-N'-(3-fluoro)benzylamide.

N-Acetylalanine (3.28 g, 25 mmol) was combined with acetonitrile (100 mL) and the mixture was placed into an ice/salt bath at −5° C. Triethylamine (2.53 g, 3.5 mL, 25 mmol) was added dropwise followed by the addition of ethyl chloroformate (2.71 g, 2.40 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0° C. The mixture was then stirred at −5° C. for 20 minutes. 3-Fluorobenzylamine (3.58 g, 28 mmol) and acetonitrile (5 mL) was added dropwise and was stirred at −5° C. for one hour and then at room temperature for 18 hours. The reaction became homogenous during this time interval.

The solution was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (100 mL) and cooled in the freezer for 3 hours resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo and identified as triethylammonium hydrochloride (3.51 g, mp 253°–257° C.). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from chloroform/diethyl ether.

Yield: 3.22 g (54%).

mp 120°–121° C.

$^1$H NMR (DMSO-$d_6$): δ 1.27 (d,J=7.1 Hz, 3H), 1.90 (s, 3H), 4.23–4.41 (m, 1H), 4.33 (d,J=6.1 Hz, 2H), 7.05–7.37 (m, 4H), 8.19 (d,J=7.1 Hz, 1H), 8.53 (t,J=6.1 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 17.9, 22.4, 41.5, 48.5, 113.3 (d,J=20.4 Hz), 113.5 (d,J=21.7 Hz), 122.8, 130.1 (d,J=7.9 Hz), 142.4 (d,J=7.4 Hz), 162.3 (d,J=243.6 Hz), 169.6, 172.8 ppm.

IR (KBr): 3280, 1645, 1545, 1450, 745, 680 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 238 (18), 151 (22), 124 (49), 114 (47), 109 (100), 87 (76), 72 (27).

Elemental analysis Calculated 60.48% C; 6.36% H; 11.76% N. Found 60.55% C; 6.32% H; 11.71% N.

## EXAMPLE 14

Preparation of D,L-α-Acetamido-N-benzyl-3-thiopheneacetamide.

D,L-α-Acetamido-3-thiopheneacetic acid (2.99 g, 15 mmol) was combined with acetonitrile (60 mL) and the mixture was placed into an ice/salt water bath (−5° C.). Triethylamine (1.51 g, 2.10 mL, 15 mmol) was added dropwise, followed by ethyl chloroformate (1.63 g, 1.43 mL, 15 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0° C. The mixture was then stirred at −5° C. (20 min). Benzylamine (1.77 g, 1.80 mL, 16.5 mmol) in acetonitrile (10 mL) was added dropwise and the mixture was stirred at −5° C. (1 h) and then room temperature (18 h). The mixture was concentrated in vacuo and the residue was combined with hot

tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride ($^1$H NMR analysis). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from 1:1 95% ethanol/water.

Yield: 1.91 g (44%).

mp 198°–199° C.

$^1$H NMR (DMSO-$d_6$): δ 1.91 (s, 3H), 4.29 (d,J=5.2 Hz, 2H), 5.61 (d,J=7.9 Hz, 1H), 7.15–7.50 (m, 3H), 8.55 (d,J=7.9 Hz, 1H), 8.74 (t,J=5.2 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 22.3, 42.0, 52.5, 122.4, 126.1, 126.7, 127.0 (3C), 128.2 (2C), 139.0, 139.2, 169.0, 169.8 ppm.

IR (KBr): 3460, 1675, 1570, 1400, 720, 695 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 288 (2), 245 (3), 155 (88), 112 (100), 91 (31), 85 (17), 65 (7).

Elemental analysis Calculated for $C_{15}H_{16}N_2O_2S$ 62.48% C; 5.59% H; 9.71% N. Found 62.41% C; 5.47% H; 9.55% N.

## EXAMPLE 15

Preparation of D,L-α-Acetamido-N-benzyl-2-thiopheneacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (6.26 g, 25 mmol) was combined with dry ether (175 mL) and then boron trifluoride etherate (5.68 g, 5.0 mL, 40 mmol) was added dropwise, resulting in a homogeneous solution. After stirring a short time, a small amount of a yellow oil separated from the solution. Thiophene (8.41 g, 8.0 mL, 100 mmol) was then added dropwise via syringe and the reaction was stirred at room temperature (4 d). The mixture was cooled in an ice bath and cold aqueous saturated $NaHCO_3$ (200 mL) was added and the aqueous layer was extracted with ethyl acetate (2×100 mL). The organic washings and the original ether layer were combined, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography, using 94:6 chloroform/methanol as an eluant ($R_f$=0.7 94:6 chloroform/methanol), and then recrystallized from benzene.

Yield: 2.67 g (37%).

mp 167°–16° C.

$^1$H NMR (DSMO-$d_6$): δ 1.91 (s 3H) 4.31 (d,J=6.0 Hz, 2H), 5.74 (d,J=7.9 Hz, 1H), 6.99–7.44 (m, 8H), 8.64 (d,J=7.9 Hz, 1H), 8.85 (t,J=6.0 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$): 22.4, 42.3, 52.2, 125.6, 125.8, 126.6, 126.9, 127.3 (2C), 128.3 (2C), 139.0, 141.4, 169.2, 169.3 ppm.

Mass spectrum, m/e (relative intensity): 289 (2), 181 (6), 155 (100), 112 (100), 91 (100), 85 (34), 74 (24).

Elemental analysis Calculated for $C_{15}H_{16}N_2O_2S$ 62.48% C; 5.59% H; 9.71% N. Found 62.64% C; 5.73% H; 9.61% N.

## EXAMPLE 16

Preparation of D,L-α-Acetamido-N-benzyl-2-furanacetamide.

N-Acetyl-D,L-2-(2-furyl)glycine (0.47 g, 2.56 mmol) was combined with acetonitrile (10 mL) and cooled to −5° C. (ice/salt water bath). Triethylamine (0.26 g, 0.36 mL, 2.56 mmol) was then rapidly added and the mixture stirred at −5° C. (3 min). Ethyl chloroformate (0.28 g, 0.25 mL, 2.56 mmol) was added dropwise between −4° C. and −3° C., and the resulting suspension was stirred at −4° C. (20 min), and then an acetonitrile solution (2 mL) of benzylamine (0.30 g, 0.31 mL, 2.82 mmol) was carefully added. During the addition of benzylamine the temperature of the solution did not go above 0° C. The mixture was stirred at −5° C. (1 h) and at room temperature (18 h), and then concentrated in vacuo. The residue was then triturated with hot tetrahydrofuran (5 mL), cooled at −16° C. (3 h), and the resulting white precipitate was filtered and identified as triethylamine hydrochloride ($^1$H NMR, 60 MHz, δ 1.00 (t,J=7.5 Hz, $CH_3$), 2.82 (q,J=7.5 Hz, $CH_2$), 3.83 (s, NH)). The filtrate was evaporated to dryness in vacuo and the resulting oil purified by flash chromatography (98:2 chloroform/methanol) to give 0.09 g (13%) of the desired product as a white solid: $R_f$ 0.30 (98:2 chloroform/methanol).

mp 178°–179° C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 1.90 (s, $CH_3$), 4.31 (d,J=6.0 Hz, $CH_2$), 5.58 (d,J=8.1 Hz, CH), 6.27–6.33 (m, $C_3$'H), 6.40–6.44 (m, $C_4$'H), 7.20–7.36 (m, Ph), 7.60–7.64 (m, $C_5$'H), 8.57 (d,J=8.1 Hz, NH), 8.73 (t,J=6.0 Hz, NH).

$^{13}$C NMR (300 MHz, DMSO-$d_6$): 22.35 ($CH_3$), 42.27 ($CH_2$), 50.95 (CH), 107.60 ($C_3$'), 110.55 ($C_4$'), 126.82 ($2C_2$" or $2C_3$"), 127.08 ($2C_2$" or $2C_3$"), 128.27 ($C_4$"), 139.05 ($C_1$"), 142.58 ($C_5$'), 151.16 ($C_2$'), 168.02 ($CH_3CO$), 169.30 (NHCO) ppm.

IR (KBr): 3230, 1625 (br), 1525 (br), 1375 (br), 1230, 1090, 890 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 273 (1), 139 (100), 96 (94), 91 (51), 65 (9).

Elemental analysis Calculated for $C_{15}H_{16}N_2O_3$ 66.16% C; 5.83% H; 10.29% N. Found 65.92% C; 5.83% H; 10.15% N.

## EXAMPLE 17

Preparation of D,L-α-Acetamido-N-benzyl-2-pyrroleacetamide.

2-Acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether (60 mL), and then boron trifluoride etherate (1.82 g, 1.57 mL, 12.8 mmol) was added in one portion and the resulting solution was stirred (15 min). The pyrrole (2.14 g, 2.22 mL, 32 mmol) was then added in one portion and the solution was stirred at room temperature (48 h) during which time a precipitate formed. Hexanes (80 mL) were then added to the suspension, and the mixture was filtered and the brown semi-solid was triturated with 95:5 chloroform/methanol (30 mL) to furnish a green solid. This material was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.94 g (35%) of the desired product as a white solid: $R_f$ 0.29 (96:4 chloroform/methanol).

mp 174°–175° C.

$^1$H NMR (300 MHz, $CD_3CN$): δ 1.93 (s, $CH_3$), 4.35 (d,J=6.0 Hz, $CH_2$), 5.42 (d,J=6.9 Hz, CH), 6.00–6.18 (m, $C_3$'H, $C_4$'H), 6.68–6.72 (m, $C_5$'H), 7.04 (d,J=6.9 Hz, NH), 7.1.7 (t,J=6.0 Hz, NH), 7.10–7.47 (m, Ph), 9.10–9.80 (br s, NH).

$^{13}$C NMR (300 MHz, $CD_3CN$): 23.02 ($CH_3$), 43.83 ($CH_2$), 52.65 (CH), 107.57 ($C_3$'), 108.85 ($C_4$'), 119.33 ($C_5$'), 127.96 ($C_2$'), 128.01 ($2C_2$" or $2C_3$"), 128.09 ($2C_2$" or $2C_3$"), 129.49 ($C_4$"), 140.01 ($C_1$"), 170.94 ($COCH_3$), 171.21 (CONH) ppm.

IR (KBr): 3320, 1570 (br), 1470 (br), 1330, 1230, 950, 890, 860, 760, 710, 690, 655 cm$^{-1}$.

Mass spectrum, m/e (relative intensity): 171 (12), 228 (2), 213 (1), 180 (2), 164 (9), 137 (93), 108 (20), 95 (100), 91 (38), 82 (35), 68 (15).

High resolution mass spectral analysis Calculated for $C_{15}H_{17}N_3O_2$ 271.13208. Found 271.13144.

## EXAMPLE 18

Preparation of D,L-2-Acetamido-N-benzyl-2-ethoxyacetamide.

An ethanolic solution (420 mL) of ethyl 2-acetamido-2-ethoxyacetate (27.92 g, 147 mmol) and benzylamine (23.70 g, 24 mL, 221 mmol) was stirred at 40°–45° C. for 3 days. The reaction mixture was evaporated in vacuo and the residue recrystallized (1:3.5 tetrahydrofuran/hexanes (650 mL)) to yield 25.80 g (70%) of the desired product as beige crystals: $R_f$ 0.59 (95:5 chloroform/methanol).

mp 153°–155° C.

$^1$H NMR (300 MHz, $CDCl_3$): δ 1.20 (t,J=7.0 Hz, $CH_3$), 2.07 (s, $CH_3$), 3.60–3.76 (m, $CH_2CH_3$), 4.40–4.54 (m, $CH_2NH$), 5.60 (d,J=8.7 Hz, CH), 6.63 (d,J=8.7 Hz, NH), 7.00 (br s, NH), 7.26–7.36 (m, Ph).

$^{13}$C NMR (300 MHz, $CDCl_3$): 15.06 ($CH_3CH_2$), 23.25 ($CH_3CO$), 43.60 ($CH_2NH$), 64.51 ($CH_2CH_3$), 77.43 (CH), 127.69 ($2C_2$" or $2C_3$", $C_4$"), 128.79 ($2C_2$" or $2C_3$"), 137.57 ($C_1$"), 168.13 ($COCH_3$), 171.29 (CONH) ppm.

IR (KBr): 3260, 1630 (br), 1550 (sh), 1505 (br), 1380, 1360, 1230, 1115, 1060, 1015, 890, 745, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 251 (4), 163 (9), 116 (98), 106 (34), 91 (98), 74 (100).

Elemental analysis Calculated for $C_{13}H_{18}N_2O_3$ 62.38% C; 7.25% H; 11.19% N. Found 62.49% C; 7.27% H; 11.24% N.

## EXAMPLE 19

Preparation of D,L-2-Acetamido-N-benzyl-2-methoxyacetamide.

To a methanolic solution (180 mL) of methyl 2-acetamido-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50° C. (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2×) to give 7.67 g (32%) of the desired product as beige crystals: $R_f$ 0.35 (95:5 chloroform/methanol).

mp 145°–146° C.

$^1$H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, $CH_3CO$), 3.37 (s, $CH_3O$), 4.40–4.35 (m, $CH_2$), 5.52 (d,J=8.7 Hz, CH), 7.12 (d,J=8.7 Hz, NH), 7.20–7.40 (m, Ph, NH).

$^{13}$C NMR (300 MHz, $CDCl_3$): 23.03 ($CH_3CO$), 43.51 ($CH_2$), 55.84 ($CH_3O$), 78.94 (CH), 127.62 ($C_4$"), 127.70 ($2C_2$" or $2C_3$"), 128.70 ($2C_2$" or $2C_3$"), 137.45 ($C_1$"), 166.91 ($COCH_3$), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050, 935, 890, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1) 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61 (100).

Elemental analysis Calculated for $C_{12}H_{16}N_2O_3$ 61.00%. C; 6.83% H; 11.86% N. 60.91% C; 6.85% H; 11.66% N.

## EXAMPLE 20

Preparation of (D,L)-α-Acetamido-N-benzyl-2-(5-methylfuran)acetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether, and then boron trifluoride etherate (1.82 g, 12.8 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The 2-methylfuran (2.63 g, 32.0 mmol) was then added and the reaction was stirred at room temperature (3 d). The reaction mixture was poured into an aqueous saturated $NaHCO_3$ solution and extracted with ethyl acetate (3×). The ethyl acetate extracts were combined, dried ($Na_2SO_4$) and evaporated in vacuo to give a beige solid, which was purified by flash chromatography (98:2 chloroform/methanol) to give the desired product as a white crystalline solid.

Yield: 1.40 g (61%)

$R_f$ 0.25 (98:2 chloroform/methanol).

mp 148°–150° C.

$^1$H NMR (DMSO-$d_6$) δ 1.88 (s, $CH_3CO$), 2.23 (s, $CH_3$), 4.24–4.36 (m, $CH_2$), 5.49 (d, J=8.0 Hz, CH), 6.01 (br s, $C_3$'H), 6.14 (d, J=2.4 Hz, $C_4$'H), 7.20–7.31 (m, Ph), 8.52 (d, J=8.0 Hz, NH), 8.69 (t, J=5.6 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 13.44 ($CH_3$), 22.35 ($CH_3CO$), 44.11 ($CH_2$), 53.23 (CH), 107.51 ($C_3$' or $C_4$'), 110.40 ($C_3$' or $C_4$'), 128.13 ($C_4$"), 128.18 ($2C_2$" or $2C_3$"), 129.43 ($2C_2$" or $2C_3$"), 139.69 ($C_1$"), 149.18 ($C_2$' or $C_5$'), 153.81 ($C_2$' or $C_5$'), 170.78 ($CH_3CO$), 173.03 (CONH) ppm.

IR (KBr) 3270, 1620 (br), 1520 (br), 1440, 1360, 1210, 1010 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 286 (3), 179(8), 153 (57), 152 (57), 111 (23), 110 (100), 97 (23), 91 (31).

Elemental Analysis Calculated: 67.12% C; 6.34% H; 9.78% N. Found: 66.92% C; 6.52% H; 9.52% N.

## EXAMPLE 21

Preparation of (D,L)-α-Acetamido-N-benzyl-2-benzofuranacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (30 mL) and then boron trifluoride etherate (0.91 g, 63 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzofuran (1.89 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The reaction mixture was poured into an ice-cold saturated aqueous solution of $NaHCO_3$, and then the mixture was maintained at this temperature for an additional 15 min. The mixture was extracted with ethyl acetate (2×), and the organic layers were combined, dried ($Na_2SO_4$) and evaporated in vacuo. The residue was purified by flash chromatography (100% chloroform, then 99:1 chloroform/methanol) to yield the desired product.

Yield: 0.43 g (33%).

$R_f$ 0.30 (98:2 chloroform/methanol).

mp 195°–196° C.;

$^1$H NMR (DMSO-$d_6$) δ 1.94 (s, $CH_3CO$), 4.34 (d, J=5.7 Hz, $CH_2$), 5.77 (d, J=8.1 Hz, CH), 7.24–7.32 (m, $C_3$'H, $C_5$'H, $C_6$'H, Ph), 7.54 (d, J=7.0 Hz, $C_4$'H or $C_7$'H), 7.62 (d, J=7.0 Hz, $C_4$'H or $C_7$'H), 8.74 (d, J=8.1 Hz, NH), 8.86 (t, J=5.7 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.27 ($CH_3CO$), 42.30 ($CH_2$), 51.22 (CH), 104.34 ($C_3$'), 110.90 ($C_7$'), 121.05 ($C_4$'), 122.90 ($C_5$'), 124.28 ($C_6$'), 126.73 ($C_{3'a}$), 127.01 ($2C_2$" or $2C_3$"), 127.69 ($2C_2$" or $2C_3$"), 128.14 ($C_4$"), 138.87 ($C_1$"), 154.10 ($C_{7'a}$), 154.30 ($C_2$'), 167.40 ($CH_3CO$), 169.26 (CONH) ppm.

IR (KBr) 3230, 1625 (br), 1520 (br), 1440, 1090, 1085, 890, 785, 690 $cm^{-1}$;

Mass spectrum, m/e (relative intensity) 322 (5), 279 (1), 264 (1), 234 (1), 215 (5), 189 (45), 146 (100), 130 (11), 118 (7), 91 (87), 65 (16).

High resolution mass spectrum, Calcd for $C_{19}H_{18}N_2O_3$ 322.1317. Found 322.1318.

## EXAMPLE 22

Preparation of (D,L)-α-Acetamido-N-benzyl-2-benzo[b] thiopheneacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (15 mL) and then boron trifluoride etherate (0.91 g, 6.3 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzo[b]thiophene (2.14 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The solution was poured into an ice-cold saturated aqueous solution of $NaHCO_3$, and then stirred for 15 min at 0° C. The mixture was extracted with ethyl acetate (2×), and the organic layers were combined, dried ($Na_2SO_4$) and evaporated in vacuo to give an orange oil. The oil was triturated with ethyl ether to yield a crystalline product which was filtered and further purified by flash chromatography (99:1 cbloroform/methanol) to give the desired product.

Yield: 0.06 g (4%).

$R_f$ 0.32 (99:1 chloroform/methanol).

mp 226°–227° C.

$^1$H NMR (DMSO-$d_6$) δ 1.94 (s, $CH_3CO$), 4.34 (d, J=5.7 Hz, $CH_2$), 5.86 (d, J=8.1 Hz, CH), 7.20–7.38 (m, $C_3$'H, $C_6$'H, $C_7$'H, Ph), 7.77–7.80 (m, $C_4$'H or $C_5$'H), 7.89–7.93 (m, $C_4$'H or $C_5$'H), 8.76 (d, J=8.1 Hz, NH), 8.97 (t, J=5.7 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.34 ($CH_3CO$), 42.38 ($CH_2$), 52.70 (CH), 122.15 ($C_4$' or $C_7$'), 122.32 ($C_4$' or $C_7$'), 123.45 ($C_3$'), 124.37 ($C_5$' or $C_6$'), 124.41 ($C_5$' or $C_6$'), 126.89 ($C_4$''), 127.27 ($2C_2$'' or $2C_3$''), 128.27 ($2C_2$'' or $2C_3$''), 138.84 ($C_{3'a}$ or $C_{7'a}$), 138.95 ($C_{3'a}$ or $C_{7'a}$), 142.58 ($C_1$'), 168.65 ($CH_3CO$), 169.12 (CONH) ppm. [A distinct signal for the $C_2$' carbon was not detected and is presumed to coincide with the $C_1$' carbon at 142.58 ppm.].

IR (KBr) 3240, 1610 (br), 1510 (br), 1420, 1360, 1215, 1085, 885, 730, 710, 685 cm$^{-1}$.

Mass spectrum, m/e (relative intensity) 338 (8), 295 (2), 205 (76), 162 (100), 135 (22), 108 (12), 91 (59).

Elemental Analysis: Calculated: 67.43% C; 5.36% H; 8.28% N. Found: 67.21% C; 5.37 % H; 8.12% N.

## EXAMPLE 23

Preparation of (D,L)-α-Acetamido-N-benzyl-3-indoleacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (0.69 g, 2.78 mmol) was suspended in anhydrous ethyl ether (20 mL) and then boron trifluoride etherate (0.63 g, 4.40 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The indole (1.30 g, 11.00 mmol) was then added and the reaction was stirred at room temperature (22 h). Petroleum ether (35°–60° C.) was added to the reaction, and the resulting semisolid material filtered, and washed with petroleum ether (35°–60° C.). Purification of the reaction mixture was accomplished by flash chromatography (98:2 chloroform/methanol) to produce the title compound as a white solid.

Yield: 0.25 g (18%).

$R_f$ 0.14 (95:5 chloroform/methanol)

mp 213°–214° C.

$^1$H NMR (DMSO-$d_6$) δ 1.90 (s, $CH_3CO$), 4.36 (d, J=6.0 Hz, $CH_2$), 5.72 (d, J=7.2 Hz, CH), 6.90–7.37 (m, Ph, $C_2$'H), 7.02 (dd, J=7.5 Hz, J=7.5 Hz, $C_5$'H or $C_6$'H), 7.12 (dd, J=7.5 Hz, J=7.5 Hz, $C_5$'H or $C_6$'H), 7.39 (d, J=7.5 Hz, $C_4$'H or $C_7$'H), 7.65 (d, J=7.5 Hz, $C_4$'H or $C_7$'H), 7.86 (d, J=7.2 Hz, NHCH), 8.13 (t, J=6.0 Hz, $NHCH_2$), 10.30–10.80 (br s, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.32 ($CH_3CO$), 42.23 ($CH_2$), 49.98 (CH), 111.51 ($C_7$'), 112.08 ($C_3$'), 118.76 ($C_4$' or $C_6$'), 119.24 ($C_4$' or $C_6$'), 121.37 ($C_5$'), 123.94 ($C_2$'), 126.58 ($C_{3'a}$), 126.71 ($C_4$''), 127.33 ($2C_2$'' or $2C_3$''), 128.18 ($2C_2$'' or $2C_3$''), 136.28 ($C_{7'a}$), 139.44 ($C_1$''), 169.13 ($CH_3CO$), 170.81 (CONH) ppm.

IR (KBr) 3260, 1610 (br), 1515 (br), 1450, 1420, 1370, 1350, 1235, 1095, 895, 735, 715, 695, 600 cm$^{-1}$.

Mass spectrum, m/e (relative intensity 321 (5), 278 (1), 264 (1), 233 (1), 214 (6), 187 (85), 171 (3), 145 (100), 118 (18), 91 (39).

Elemental Analysis: Calculated: 71.01% C; 5.96% H; 13.06% N. Found: 70.87% C; 6.15% H; 12.78% N.

## EXAMPLE 24

Preparation of (D,L)-α-Acetamido-N-benzyl-2-(5-methylpyrrole)acetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8 mmol) was suspended in anhydrous ethyl ether (175 mL), and then boron trifluoride etherate (1.38 g, 9.7 mmol) was added and the resulting solution stirred (15 min). The 2-methylpyrrole (0.85 g, 10 mmol) was then added and the reaction mixture was stirred under $N_2$ (6 d), during which time the color of the reaction mixture turned reddish brown and a dark-brown deposit formed at the bottom of the flask. The clear solution was decanted and treated with an aqueous saturated $NaHCO_3$ solution containing ice (100 mL) for 30 min. The aqueous reaction mixture was extracted with ethyl acetate (3×30 mL). The combined extracts were dried ($Na_2SO_4$) and the solvent removed in vacuo. The brown oily residue was purified by flash column chromatography using 98:2 chloroform/methanol as the eluent to yield the desired compound. The product was recrystallized from ethyl acetate/hexane to give a light yellow amorphous solid.

Yield 0.20 g (94%)

$R_f$ 0.44 (95:5, chloroform/methanol).

mp 167°–168° C.

$^1$H NMR (DMSO-$d_6$) δ 1.87 (s, $CH_3$), 2.13 (s, $COCH_3$), 4.27 (br s, $CH_2$), 5.33 (d, J=7.4 Hz, CH), 5.60 (s, $C_4$H), 5.77 (s, $C_3$H), 7.19–7.30 (m, 5 PhH), 8.22 (d, J=7.4 Hz, NH), 8.45 (t, J=5.5 Hz, NH), 10.38 (s, NH).

$^{13}$C NMR (DMSO-$d_6$) 12.74 ($CH_3$), 22.49 ($COCH_3$), 42.11 ($CH_2$), 51.21 (CH), 105.09 ($C_4$), 106.07 ($C_3$), 126.16 ($C_5$), 126.64 ($C_4$'), 126.85 ($C_2$), 127.09 ($2C_2$' or $2C_3$'), 128.17 ($2C_2$' or $2C_3$'), 139.33 ($C_1$'), 168.88 ($COCH_3$), 169.79 (CONH) ppm.

IR (KBr) 3250, 1630, 1520, 1420, 1360, 1300, 1260, 1230, 1160, 1110, 1020 cm$^{-1}$.

Mass spectrum, m/e (relative intensity) 285 ($M^+$, 10), 178 (20), 152 (24), 151 (100), 110 (12), 109 (93), 108 (22), 107 (25), 94 (16), 91 (43).

Elemental Analysis: Calculated: 67.35% C; 6.71% H; 14.73% N. Found: 67.57% C; 6.90% H; 14.52% N.

Synthesis of Unsubstituted and Substituted-α-Acetamido-N-benzyl-2-furanacetamides.

General Procedure.

4-Methylmorpholine (1 equiv) was added to a solution of α-acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at −10° to −15° C. under $N_2$. After stirring (2 min), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was

allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10 mL/10 mmol) was added over 5 min at −10° to −15° C. The reaction mixture was allowed to stir at room temperature for 5 min and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated in vacuo, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization, or flash chromatography of the combined solid material. Examples 25–32 were prepared according to this procedure.

## EXAMPLE 25

(D,L-α-Acetamido-N-benzyl-2-furanacetamide.

Using benzyl amine (0.27 g, 2.56 mmol) and racemic α-acetamido-2-furanacetic acid (0.47 g, 2.56 mmol) gave the desired compound. The product was recrystallized from ethyl acetate to give a white solid.

Yield: 0.46 g (65%)

$R_f$ 0.30 (98:2 chloroform/methanol).

mp 177°–178° C.

$^1$H NMR (DMSO-$d_6$) δ 1.90 (s, $CH_3$), 4.31 (d, J=6.0 Hz, $CH_2$), 5.58 (d, J=8.1 Hz, CH), 6.27–6.33 (m, $C_3$H), 6.40–6.44 (m, $C_4$H), 7.20–7.36 (m, 5 PhH), 7.60–7.64 (m, $C_5$H), 8.57 (d, J=8.1 Hz, NH), 8.73 (t, J=6.0 Hz, NH).

## EXAMPLE 26

(D,L)-α-Acetamido-N-(2-fluorobenzyl)-2-furanacetamide.

Using 2-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic α-acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.

Yield: 120 g (50%).

$R_f$ 0.36 (94:4 chloroform/methanol).

mp 193°–195° C. (recrystallized from EtOAc).

$^1$H NMR (DMSO-$d_6$) δ 1.89 (s, $COCH_3$), 4.33 (d, J=5.5 Hz, $CH_2$), 5.58 (d, J=80 Hz, CH), 6.28 (s, $C_4$H), 6.29 (s, $C_3$H), 7.62 (s, $C_5$H), 7.13–7.35 (m, 4 ArH), 8.61 (d, J=80 Hz, NH), 8.76 (t, J=5.5 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.35 ($COCH_3$), 36.12 (d, $J_{CF}$=6.6 Hz, $CH_2$), 50.88 (CH), 107.64 ($C_4$), 110.43 ($C_3$), 115.04 (d, $J_{CF}$=21.4 Hz, $C_{3'}$), 124.29 (d, $J_{CF}$=4.2 Hz, $C_{5'}$), 125.64 (d, $J_{CF}$=15.0 Hz, $C_{1'}$), 128.94 (d, $J_{CF}$=9.0 Hz, $C_{4'}$ or $C_{6'}$), 129.27 (d, $J_{CF}$=5.5 Hz, $C_{4'}$ or $C_{3'}$), 142.66 ($C_5$), 151.07 ($C_2$), 159.99 (d, $J_{CF}$=244.4 Hz, $C_{2'}$), 168.17 ($COCH_3$), 169.24 (CONH) ppm.

IR (KBr) 3270, 1630, 1520, 1440, 1360, 1220, 1180, 1140, 1100, 1000, 740 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 291 ($M^+$+1, 3), 274 (2), 247(3), 165 (4), 145 (10), 139 (98), 138 (46), 126 (7), 110 (10), 109 (65), 97 (93), 96 (100).

Elemental Analysis: Calculated: 62.02% C; 5.21% H; 9.65% N. Found: 62.20% C; 5.19% H; 9.69% N.

## EXAMPLE 27

(D,L)-α-Acetamido-N-(3-fluorobenzyl)-2-furanacetamide.

Making use of 3-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic α-acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.

Yield 1.90 g (80%).

$R_f$ 0.30 (96:4 chloroform/methanol).

mp 163°–165° C. (recrystallized from ethyl acetate).

$^1$H NMR (DMSO-$d_6$) δ 1.89 (s, $COCH_3$), 4.31 (d, J=5.5 Hz, $CH_2$), 5.55 (d, J=7.8 Hz, CH, 6.31 (s, $C_4$H), 6.42 (s, $C_3$H), 6.98–7.37 (m, 4 ArH), 7.62 (s, $C_5$H), 8.61 (d, J=7.8 Hz, NH), 8.70 (t, J=5.5 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.35 ($COCH_3$), 41.71 ($CH_2$), 51.01 (CH), 107.73 ($C_4$), 110.59 ($C_3$), 113.50 (d, $J_{CF}$=21.6 Hz, $C_{2'}$ or $C_{4'}$), 113.60 (d, $J_{CF}$=22.3 Hz, $C_{2'}$ or $C_{4'}$), 122.95 (br, $C_{6'}$), 130.18 (d, $J_{CF}$=8.6 Hz, $C_{5'}$), 142.21 (d, $J_{CF}$=7.5 Hz, $C_{1'}$), 142.66 ($C_5$), 151.03 ($C_2$), 162.28 (d, $J_{CF}$=243.3 Hz, $C_{3'}$), 168.23 ($COCH_3$), 169.31 (CONH) ppm.

IR (KBr) 3230, 1630, 1540, 1440, 1360, 1220, 1140, 1000, 730 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 290 ($M^+$,71), 231 (7), 165 (18), 140 (23), 130 (100), 126 (16), 109 (6), 97 (118), 96 (100), 96 (30).

Elemental analysis: Calculated: 62.02% C; 5.21% H, 9.65% N. Found: 61.97% C; 5.35% H; 9.53% N.

## EXAMPLE 28

(D,L)-α-Acetamido-N-(4-fluorobenzyl)-2-furanacetamide.

Using racemic α-acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) and 4-fluorobenzylamine (1.13 g, 9.0 mmol) gave the desired product.

Yield 2.10 g (88%).

$R_f$ 0.30 (96:4 chloroform/methanol).

mp 188°–190° C. (recrystallized from ethyl acetate).

$^1$H NMR (DMSO-$d_6$) δ 1.88 (s, $COCH_3$), 4.27 (d, J=5.5 Hz, $CH_2$), 5.55 (d, J=8.0 Hz, CH), 6.27 (s, 1H), 6.41 (s, 1H), 7.09–7.15 (m, 2ArH), 7.12–7.27 (m, 2 ArH), 7.61 (s, 1H), 8.58 (d, J=8.0 Hz, NH), 8.75 (t, J=5.5 Hz, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.28 ($COCH_3$), 41.51 ($CH_2$), 50.87 (CH), 107.52 ($C_4$), 110.46 ($C_3$), 114.90 (d, $J_{CF}$=21.1 Hz, $C_{3'}$), 129.48 (d, $J_{CF}$=8.3 Hz, $C_{2'}$), 135.23 (d, $J_{CF}$=3.2 Hz, $C_{1'}$), 142.53 ($C_5$), 151.08 ($C_2$), 161.12 (d, $J_{CF}$=242.2 Hz, $C_{4'}$), 167.95 ($COCH_3$), 169.13 (CONH) ppm.

IR (KBr) 3230, 1620, 1500, 1360, 1320, 1260, 1210, 1140, 1000, 820, 780, 730 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 291 ($M^+$1, 4), 165, (4), 140 (9), 139 (92), 138 (52), 124 (6), 109 (71), 97 (60), 96 (100).

Elemental Analysis: Calculated: 62.02% C; 5.21% H; 9.65% N. Found: 61.76% C; 5.41% H; 9.43% N.

## EXAMPLE 29

(D,L)-α-Acetamido-N-(2,5-difluorobenzyl)-2-furanacetamide.

Using 2,5-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic α-acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.

Yield 1.60 g (64%).

$R_f$ 0.38 (96:4 chloroform/methanol).

mp 177°–178° C. (recrystallized from ethyl acetate).

$^1$H NMR (DMSO-$d_6$) δ 1.89 (s, $COCH_3$), 4.31 (d, J=5.5 Hz, $CH_2$), 5.55 (d, J=7.7 Hz, CH), 6.32 (s, $C_4$H), 6.43 (s, $CH_3$H), 7.22–7.25 (m, 3 ArH), 7.62 (s, $C_5$H), 8.62 Hz, NH), 8.78 (t, J=5.5 H, NH).

$^{13}$C NMR (DMSO-$d_6$) 22.30 ($COCH_3$), 35.98 (d, $J_{CF}$=5.8 Hz, $CH_2$), 51.02 (CH), 107.81 ($C_4$), 110.58 ($C_3$), 115.06 (dd, $J_{CF}$=19.5, 25.6 Hz, $C_{3'}$ or $C_{6'}$), 115.16 (dd, $J_{CF}$=15.6, 24.7 Hz, $C_{3'}$ or $C_{6'}$), 116.52 (dd, $J_{CF}$=10.1, 23.9 Hz, $C_{4'}$), 127.98 (dd, $J_{CF}$=9.2, 17.7 Hz, $C_{1'}$), 142.69 ($C_5$), 150.78 ($C_2$), 155.89 (d, $J_{CF}$=239.0 Hz, $C_{2'}$ or $C_{5'}$), 158.18 (d, $J_{CF}$=238.8 Hz, $C_{2'}$ or $C_{5'}$), 168.38 ($COCH_3$), 169.35 (CONH) ppm.

IR (KBr) 3230, 1620, 1520, 1480, 1360, 1260, 1230, 1180, 1140, 1000, 860, 810, 730, 710 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 309 ($M^+$+1, 1), 266 (1), 222(1), 165 (5), 140 (5), 139 (61), 138 (36), 127 (37), 97 (44), 96 (100).

Elemental Analysis: Calculated: 58.44% C; 4.58% H; 9.09% N. Found: 58.68% C; 4.69% H; 8.87% N.

## EXAMPLE 30

(D,L)-α-Acetamido-N-(2,6-difluorobenzyl)-2-furanacetamide.

Making use of 2,6-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic α-acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) the desired product was form

Yield 1.90 g (73%).

mp 237°–239° C. (recrystallized from ethanol).

$^1H$ NMR (DMSO-$d_6$) δ 1.86 ($COCH_3$), 4.33 (d, J=4.5 Hz, $CH_2$), 5.53 (d, J=8.3 Hz, CH, 6.17 (s, $C_4H$), 6.38 (s, $C_3H$), 7.05–7.10 (m, 2 ArH, 7.36–7.41 (m, 1 ArH, 7.60 (s, $C_5H$), 8.52 (d, J=8.3 Hz, NH), 8.66 (t, J=4.5 Hz, NH).

$^{13}C$ NMR (DMSO-$d_6$) δ 22.33 ($COCH_3$), 30.74 (t, $J_{CF}$= 4.4 Hz, $CH_2$), 50.48 (CH), 107.24 ($C_4$), 110.40 ($C_3$), 111.61 (dd, $J_{CF}$=8.0, 25.1 Hz, $C_{3'}$, $C_{5'}$), 113.67 (t, $J_{CF}$=19.5 Hz, $C_{1'}$), 129.98 (t, $J_{CF}$=10.5 Hz, $C_{4'}$), 142.50 ($C_5$), 151.23 ($C_2$), 160.93 (d, $J_{CF}$=248.1, $C_{2'}$ or $C_{6'}$), 161.10 (d, $J_{CF}$=248.1 Hz, $C_{2'}$ or $C_{6'}$), 167.59 ($COCH_3$), 169.00 (CONH) ppm.

IR (KBr) 3230, 1620, 1530, 1460, 1360, 1320, 1260, 1220, 1160, 1140, 1030, 1000, 820, 780, 750, 740, 710 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 309 ($M^+$+1, 4), 265 (2), 165 (4), 147 (7), 140 (8), 139 (87), 138 (36), 127 (54), 97 (58), 96 (100).

Elemental Analysis: Calculated: 58.44% C; 4.58% H; 9.09% N. Found: 58.62% C; 4.74H; 8.89% N.

## EXAMPLE 31

(D)-(−)α-Acetamido-N-benzyl-2-furanacetamide

Starting with D-α-acetamido-2-furanacetic acid (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), the desired product was obtained.

Yield: 2.54 g (70%) The product was further recrystallized from ethyl acetate to give the title compound

Yield: 2.30 g

mp 196°–197° C.

$[\alpha]^{26}_{D[c=1,\ MeOH]}$=−78.3°. Addition of R(−)-mandelic acid to a $CDCl_3$ solution of the product gave only one signal for the acetamide methyl protons.

Mass spectrum, m/e (relative intensity) 272 ($M^+$, 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63).

Elemental Analysis: Calculated: 66.16% C; 5.92% H; 10.29% Found: 66.09% C; 6.01% H; 10.38% N.

## EXAMPLE 32

(L)-(+)-α-Acetamido-N-benzyl-2-furanacetamide.

Using L-α-acetamido-2-furanacetic acid (2.83 g, 15.46 mmol) and benzylamine (1.65 g, 15.46 mmol) gave 3.80 g of the enriched desired product. $^1H$ NMR analysis with R(−)-mandelic acid showed that it was greater than 80% enriched in the title compound. The pure L-enantiomer was obtained by recrystallization from absolute ethanol.

Yield: 1.60 g.

mp 196°–197° C.

$[\alpha]^{26}_{D[c=1,\ MeOH]}$=+79.0°.

Mass spectrum, m/e (relative intensity) 273 ($M^+$+1, 3), 229 (2), 214 (2), 184 (1), 165 (7), 157 (4), 140 (33), 139 (100), 138 (95), 97(98), 96 (100), 91 (98).

Elemental Analysis: Calculated: 66.16% C; 5.92% H; 10.29% N. Found: 65.89% C; 5.86% H; 10.42% N.

## EXAMPLE 33

Resolution of (D,L)-α-Acetamido-2-furanacetic acid Using (R)-(+)-α-Methylbenzylamine and (S)-(−)-α-Methylbenzylamine.

(R)-(+)-α-Methylbenzylamine (13.22 g, 0.11 mol) was added to an absolute ethanol solution (550 mL) of racemic α-acetamido-2-furanacetic acid (20.00 g, 0.11 mol). The resulting solution was cooled in the freezer overnight. The white precipitate (12.00 g) which separated upon cooling was filtered, and the mother liquid evaporated to give a salt which was later used for obtaining L-α-acetamido-2-furanacetic acid. The initial salt was recrystallized (3×) from absolute ethanol to yield 4.00 g of the pure diasteromeric salt.

mp 173°–175° C.

$[\alpha]^{26}$D[c=1, MeOH]=−108°.

Elemental Analysis Calculated: 63.14% C; 6.62% H; 9.21% N. Found: 63.19% C; 6.62% H; 9.12% N.

The purified salt was treated with 5% aqueous $NH_4OH$ solution, extracted with ethyl ether (3×50 mL), and then acidified with a 8.5% aqueous solution of $H_3PO_4$ and then extracted with ethyl acetate (3×100 mL) to yield 2.45 g (25%) of D-α-acetamido-2-furanacetic acid.

mp 69°–171° C.

$[\alpha]^{26}$D[c=1, MeOH]=−184.2°.

Elemental Analysis: Calculated: 52.46% C; 4.95% H; 7.65% N. Found: 52.17% C; 4.89% H; 7.56% N.

The salt obtained after evaporation of the main mother liquor was hydrolysed with 5% aqueous $NH_4OH$ solution to give 10.10 g of the enriched L-α-acetamido-2-furanacetic acid [$[\alpha]^{26}$D[c=1, MeOH]=+47.7°]. (S)-(−)-methylbenzylamine (6.70 g, 0.055 mol) was added to a solution of enriched L-α-acetamido-2-furanacetic acid (10.10 g, 0.055 mol) in absolute ethanol (275 mL). The white precipitate of the diasteroemeric salt (8.10 g) that separated upon cooling the solution in the freezer (1 h) was filtered. The salt was recrystallized from absolute ethanol (3×) to yield 3.00 g of the salt.

mp 172°–174° C.

$[\alpha]^{26}$D[c=1, MeOH]=+106°.

Elemental Analysis: Calculated: 63.14% C; 6.62% H; 9.21% N. Found: 63.18% C; 6.47% H; 9.00% N.

The salt from the third recrystallization was treated with a 5% aqueous $NH_4OH$ solution and extracted with ethyl ether (3×50 mL), and then acidified with a 8.5% aqueous solution of $H_3PO_4$, and then extracted with ethyl acetate (3×100 mL) to give 1.63 g (32%) of L-α-acetamido-2-furanacetic acid.

mp 169°–171° C.

$[\alpha]^{26}$D[c=1, MeOH]=+182°.

## EXAMPLE 34

Enzymatic Separation of D(−)α-acetamido-2-furanacetic acid (R-19) from DL (±)α-acetamido-2-furanacetic acid.

DL (±)α-acetamido-2-furanacetic acid (2.00 g, 10.9 mmol) was suspended in deionized $H_2O$ (600 mL). An

aqueous solution of LiOH (1N) was added to this suspension dropwise until all of the acid had dissolved and the pH was 7.2 Acylase 1, Grade II (20 mg, activity=900 units/mg, Sigma Chemical Company, Cat. No. A 8376) was then added to the above solution and the mixture stirred at 34°–37° C. (41 h). The suspension was then cooled to room temperature and acidified to pH 1.5 with aqueous 1N HCl. The suspended material was filtered, and the filtrate was saturated with solid NaCl, and then extracted with ethyl acetate (3×250 mL). The combined ethyl acetate extracts was dried ($Na_2SO_4$). The solvent was removed in vacuo and the residue was triturated with ethyl acetate (10 mL). The white solid (0.75 g) that remained was filtered and was pure D(−)α-acetamido-2-furanacetic acid; mp 168°–169° C., mixed mp with an authentic sample 168°–169° C.; $[\alpha]_D^{26}$ [c=1, MeOH]=−184.3°.

## EXAMPLE 35

Preparation of D,L-α-Acetamido-2-furanacetic Acid.

An ethereal solution of $ZnCl_2$ (1N, 28 mL, 0.028 mol) was added to a stirred solution of ethyl acetamido-2-bromoacetate (4.40 g, 0.019 mol) and furan (11.23 g, 0.165 mol) in dry tetrahydrofuran (100 mL), and allowed to stir at room temperature (5 h). The mixture was then treated with $H_2O$ (50 mL), the organic phase separated, and the aqueous layer extracted with $CH_2Cl_2$ (2×100 mL). The organic layers were combined, dried ($Na_2SO_4$) and the volatile materials were removed by distillation in vacuo to give approximately 4.00 g (97%) of light-brown semi-solid material. TLC analysis showed a major spot at $R_f$ 0.30 (99:1 chloroform/methanol). The desired compound, D,L-ethyl α-acetamido-2-furanacetate, was purified by flash column chromatography on silica gel using 99:1 chloroform/methanol as the eluent to give 3.60 g (87%) of a beige solid.

mp 68°–70° C.

D,L-Ethyl α-acetamido-2-furanacetate (4.00 g, 19 mmol) was dissolved in 90:10 ethanol/water (150 mL) and then KOH (2.00 g, 35 mmol) was added and the resulting solution stirred at room temperature (48 h). The reaction was concentrated in vacuo and the residue diluted with $H_2O$ and then washed with ethyl ether (3×50 mL). The aqueous layer was then made acidic with a 8.5% aqueous solution of $H_3PO_4$ and extracted with ethyl acetate (3×150 mL). The organic layers were combined, dried ($Na_2SO_4$), evaporated to dryness in vacuo to give the desired compound.

Yield: 2.65 g (76%).

$R_f$ 0.37 (8:1:1 isopropanol/$NH_4OH$/$H_2O$).

mp 172°–174° C.

## EXAMPLE 36

Synthesis of (D,L)-α-Acetamido-4-pentenoic Acid-N-benzylamide.

4-Methylmorpholine (0.55 g, 5.40 mmol) was added to a stirred solution of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol) in dry tetrahydrofuran (60 mL) at −10° to −15° C. under $N_2$. After stirring (2 min), isobutyl chloroformate (0.75 g, 5.70 mmol) was added leading to the precipitation or a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of benzylamine (0.61 g, 5.70 mmol) in tetrahydrofuran (10 mL) was added slowly at −10° to −15° C. After stirring (5 min) at room temperature, the insoluble salt was removed by filtration. The filtrate was evaporated to dryness and the residue was triturated with ethyl acetate, and the remaining white solid was filtered to yield the desired product.

Yield 0.81 g (64%).

$R_f$ 0.36 (4% methanol/chloroform).

mp 118°–120° C. (recrystallized from ethyl acetate/cyclohexane).

$^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, $COCH_3$), 2.22–2.49 (m, $CH_2CH{=}CH_2$), 4.26 (d, J=5.3 Hz, $CH_2Ph$), 4.25–4.33 (m, CH), 4.99–5.09 (m, $CH_2CH{=}CH_2$), 7.21–7.29 (m, 5 PhH), 8.05 (d, J=7.6 Hz, NH), 8.46 (br s, NH).

$^{13}C$ NMR (DMSO-$d_6$) 22.41 ($COCH_3$), 36.24 ($CH_2CH{=}CH_2$), 41.91 ($CH_2Ph$), 52.20 (CH), 117.15 ($CH_2CH{=}CH_2$), 126.54 ($C_4$), 126.99 ($2C_2$ or $2C_3$), 128.04 ($2C_2$ or $2C_3$), 134.25 ($CH_2CH{=}CH_2$), 139.22 ($C_1$), 169.02 ($COCH_3$), 170.96 (CONH) ppm.

Mass spectrum, m/e (relative intensity) 246 ($M^+$, 4), 205 (4), 163 (15), 140 (8), 106 (33), 91 (77), 70 (100).

Elemental Analysis: Calculated: 68.27% C; 7.37% H; 11.37% N. Found: 68.55% C; 7.31% H; 11.48% N.

Mass spectrum m/e (relative intensity) 292 ($M^+$+1, 1), 233 (8), 158 (19), 157 (100), 116 (26), 115 (100), 106 (29), 91 (72).

Elemental Analysis: Calculated: 61.84% C; 7.26% H; 14.42% N. Found: 61.67% C; 7.10% H; 14.14% N.

## EXAMPLE 37

Synthesis or (D,L)-2-Acetamido-N-benzyl-2-(1-morpholine)acetamide.

A mixture of ethyl 2-acetamido-2-(1-morpholine)acetate (0.59 g, 2.56 mmol), benzylamine (0.28 g, 2.82 mmol) and sodium cyanide (0.01 g, 0.26 mmol) in methanol (5 mL) was stirred at 50°–55° C. for 18 hr. The solvent was removed in vacuo and the residue triturated with ethyl acetate (5 mL). The white solid (0.35 g) that remained was collected by filtration and identified as the desired compound. The filtrate was concentrated and the residue purified by flash column chromatography (2% methanol/chloroform) on $SiO_2$. The initial fractions gave a trace amount (0.09 g) or (D,L)-2-acetamido-N-benzyl-2-(N-benzylamine)acetamide. Continued elution gave additional amounts (0.20 g) of the title compound.

(D,L)-2-Acetamido-N-benzyl-2-(N-benzylamine) acetamide:

Yield: 0.09 g (11%).

mp 135°–138° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, $COCH_3$), 3.56 (d, J=13.6 Hz, NHCH), 3.66 (d, J=13.6 Hz, NHCH), 4.23 (d, J=5.4 Hz, $CH_2$), 4.89 (d, J=8.0 Hz, CH), 7.05–7.38 (m, 10 PhH), 8.20 (d, J=8.0 Hz, NH), 8.51 (t, J=5.4 Hz, NH).

$^{13}C$ NMR (DMSO-$d_6$) 22.63 ($COCH_3$), 42.11 ($CH_2$), 48.57 ($NHCH_2$), 64.41 (CH), 126.65 ($C_4$), 126.70 ($C_{4'}$), 127.13, 128.00, 128.13, 128.22, 139.24 ($C_1$ or $C_{1'}$), 140.12 ($C_1$ or $C_{1'}$), 169.61 ($COCH_3$), 169.90 (CONH) ppm.

(D,L)-2-Acetamido-N-2-benzyl-2-(1-morpholine) acetamide.

Yield: 0.48 g (64%).

$R_f$ 0.35 (4% methanol/chloroform).

mp 171°–172° (recrystallized from ethyl acetate).

$^1H$ NMR (DMSO-$d_6$) δ 1.86 (s, $COCH_3$), 2.30–2.40 (m, $CH_2NCH_2$), 3.51 (br s, $CH_2OCH_2$), 4.18–4.33 (m, $CH_2$), 5.07 (d, J=8.9 Hz, CH), 7.18–7.25 (m, 5 PhH), 8.23 (d, J=8.9 Hz, NH), 8.58 (br s, NH).

$^{13}C$ (DMSO-$d_6$) 22.39 ($COCH_3$), 42.20 ($CH_2$), 48.43 ($CH_2NCH_2$), 66.03 (CH), 69.24 ($CH_2OCH_2$), 126.76 ($C_{4'}$), 127.13 ($2C_2$ or $2C_3$), 128.23 ($2C_2$ or $2C_3$), 139.42 ($C_{1'}$),

EXAMPLE 38

Synthesis of (D,L)-Ethyl 2-acetamido-2-(ethylamino) acetate.

A cold (−78° C.) solution of ethyl 2-acetamido-2-bromoacetate (2.10 g, 9.38 mmol) in dry tetrahydrofuran (80 mL) was added slowly into a cooled (−78° C.) tetrahydrofuran (20 mL) solution of methylamine (1.40 g, 31.04 mmol) over a period of 20 min. The reaction was stirred at −78° C. (1 h), and then at room temperature (1 h). The precipitated salt was filtered and the filtrate concentrated. The residue was purified by flash column chromatography on $SiO_2$ using 3% methanol/chloroform as the eluent to yield the desired compound as a light yellow oil.

Yield: 0.90 (51%).

$R_f$ 0.36 (4% methanol/chloroform).

$^1H$ NMR ($CDCl_3$) 0.93 (t, J=6.7 Hz, $NHCH_2CH_3$), 1.12 (t, J=6.8 Hz, $OCH_2CH_3$), 1.87 (s, $COCH_3$), 2.48 (q, J=6.7 Hz, $NHCH_2CH_3$), 4.05 (q, J=6.8 Hz, $OCH_2CH_3$), 5.05 (d, J=7.1 Hz, CH), 7.09 (d, J=7.1 Hz, NH).

$^{13}C$ NMR ($CDCl_3$) 13.64 ($NHCH_2CH_3$), 14.55 ($OCH_2CH_3$), 22.53 ($COCH_3$), 39.06 ($NHCH_2CH_3$), 61.38 (CH), 64.14 ($OCH_2CH_3$), 170.09 ($COCH_3$), 170.20 ($COOCH_2CH_3$) ppm.

EXAMPLE 39

Using the procedures described herein, the following examples are also prepared:

(D,L)α-Acetamido-N-benzyl-3-furanacetamide

(D,L)α-Acetamido-N-(2-fluorobenzyl)-3-furanacetamide

(D,L)α-Acetamido-N-(3-fluorobenzyl)-3-furanacetamide

(D,L)α-Acetamide-N-(4-fluorobenzyl)-3-furanacetamide

α-Acetamide-N-benzyl-2-aminoacetamide

Preparation of α-Heteroatom Substituted Amino Acids, Synthesis of Ethyl 2-Acetamido-2-substituted Acetates.

General Procedure.

A cooled (−78° C.) solution of ethyl 2-bromo-2-acetamidoacetate (1 equiv) in THF (1 mmol/10 mL) was added slowly to a THF (1 mmol/4 mL) solution of the nitrogen nucleophile (5–10 equiv) at −78° C. The reaction was stirred at this temperature (0.5 h) and then at room temperature (1 h). The insoluble materials were filtered and washed with THF. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on $SiO_2$ gel (using the indicated solvent as the eluent) to give the desired product.

Using this procedure the following examples were prepared.

EXAMPLE 40

Synthesis of Ethyl 2-Acetamido-2-aminoacetate.

Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and liquid $NH_3$ (5–6 equiv) yielded a light brown residue, which on purification by flash column chromatography on $SiO_2$ gel (5% MeOH/$CHCl_3$) gave the desired product as a yellow oil.

Yield: 1.00 g (70%).

$R_f$ 0.21 (5% MeOH/$CHCl_3$).

$^1H$ NMR ($CDCl_3$) δ 1.31 (t, J=7.1 Hz, 3H), 2.03 (s, 3H), 2.61 (br s, 2H), 4.24 (q, J=7.1 Hz, 2H), 5.21 (d, J=7.1 Hz, 1H), 7.50 (d, J=7.1 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$) 13.72, 22.68, 59.70, 61.73, 170.40, 170.68 ppm.

EXAMPLE 41

Synthesis of Ethyl 2-Acetamido-2-(methylamino)acetate.

Use of ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and $MeNH_2$ (2.50 g, 80.6 mmol) gave an oily residue (1.50 g). The residue was purified by flash column chromatography on $SiO_2$ gel (3% MeOH/$CHCl_3$) to yield the desired product as an oil.

Yield: 1.00 g (65%).

$^1H$ NMR ($CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 2.07 (s, 3H), 2.36 (s, 3H), 4.26 (q, J=7.1 Hz, 2H), 5.20 (d, J=7.4 Hz, 1H), 6.60 (br s, 1H).

$^{13}C$ NMR ($CDCl_3$) 14.02, 23.06, 30.84, 62.04, 65.72, 170.09, 170.40 ppm.

EXAMPLE 42

Synthesis of Ethyl 2-Acetamido-2-(N,N-dimethylamino) acetate.

Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and $Me_2NH$ (5–6 equiv) gave the desired product as a yellow oil.

Yield: 1.50 g (89%).

$^1H$ NMR ($CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 2.02 (s, 3H), 2.33 (s, 6H), 4.10–425 (m, 2H), 5.24 (d, J=8.3 Hz, 1H), 6.59 (d, J=8.3 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$) 14.05, 23.00, 40.28 (2 C), 61.84, 69.24, 169.38, 170.57 ppm.

EXAMPLE 43

Synthesis of Ethyl 2-Acetamido-2-(4-morpholine)acetate.

Using morpholine (1.71 g, 19.64 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) gave an oily residue, which was purified by flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give the desired product as a thick oil.

Yield: 1.90 g (93%).

$R_f$ 0.29 (3% MeOH/$CHCl_3$).

$^1H$ NMR ($CDCl_3$) δ 1.32 (t, J.=6.8 Hz, 3H), 2.07 (s, 3H), 2.43–2.72 (m, 4H), 3.58–3.78 (m 4H), 4.26 (q, J=6.8 Hz, 2H), 5.27 (d, J=7.9 Hz, 1H), 6.39 (d, J=7.9 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$) 14.21, 23.25, 48.47 (2 C), 62.06, 66.71 (2 C), 69.22, 169.00, 170.46 ppm.

EXAMPLE 44

Synthesis of Ethyl 2-Acetamido-2-(N-anilino)acetate.

Use of aniline (1.83 g, 19.6 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) provided a brown residue which was purified by flash column chromatography on $SiO_2$ gel ($CHCl_3$-2% MeOH/$CHCl_3$ gradient) to yield the desired product.

Yield: 1.80 g (85%).

$R_f$ 0.52 (4% MeOH/$CHCl_3$).

mp 87°–89° C. (recrystallized from ethyl acetate/petroleum ether).

$^1H$ NMR ($CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H), 1.84 (s, 3H), 4.27 (q, J=7.1 Hz, 2H), 5.89 (d, J=8.2 Hz, 1H), 6.43 (d, J=8.2 Hz, 1H), 6.68–6.71 (m, 2H), 6.80–6.83 (m, 1H), 7.17–7.22 (m, 2H). The remaining amino proton was not detected.

$^{13}C$ NMR ($CDCl_3$) 13.96, 22.98, 60.19, 62.41, 113.87 (2 C), 119.29, 129.37 (2 C), 144.09, 169.77, 170.14 ppm.

IR (KBr) 3340, 1720, 1635, 1590, 1490, 730, 710 $cm^{-1}$.

Mass spectrum (FD) 237 ($M^{30}$+1).

Elemental analysis Calculated for $C_{12}H_{16}N_2O_3$ 61.00% C; 6.83% H; 11.86% N. Found 60.88% C; 6.56% H; 12.00% N.

## EXAMPLE 45

Synthesis of Ethyl 2-Acetamido-2-(N-(3-pyrazolylamino)) acetate.

Using ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.92 mmol) and 3-aminopyrazole (1.85 g, 22.32 mmol) and purification of the reaction product by chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) gave the desired product as a yellow oil.

Yield: 1.80 g (89%).

$R_f$ 0.35 (8% MeOH/$CHCl_3$).

$^1H$ NMR ($CDCl_3$) δ 1.21 (t, J=7.1 Hz, 3H), 1.89 (s, 3H), 4.20 (q, J=7.1 Hz, 2H), 5.64 (d, J=1.8 Hz, 1H), 5.71 (br s, 1H), 5.73 (d, J=7.1 Hz, 1H), 7.29 (d, J=1.8 Hz, 1H), 7.98 (d, J=7.1 Hz, 1H). The remaining amino proton was not detected.

$^{13}C$ NMR ($CDCl_3$) 13.73, 22.49, 61.41, 62.02, 91.79, 130.53, 153.02, 169.96, 170.93 ppm.

## EXAMPLE 46

Synthesis of Ethyl 2-Acetamido-2-hydroxyamino)acetate.

Using ethyl 2-bromo-2-acetamidoacetate (2.10 g, 9.37 mmol) and anhydrous $NH_2OH$ (0.93 g, 28.00 mmol) gave an oily residue. The residue was purified by flash column chromatography on $SiO_2$ gel (5% MeOH/$CHCl_3$) to give the desired product. The product was recrystallized from EtOH to give a white flaky solid.

Yield: 1.00 g (61%).

$R_f$ 0.24 (5% MeOH/$CHCl_3$).

mp 119°–121° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.19 (t, J=6.9 Hz, 3H), 1.87 (s, 3H), 4.10 (q, J=6.9 Hz, 2H), 5.09 (dd, J=4.0, 8.0 Hz, 1H), 6.06 (br s, 1H), 7.63 (s, 1H), 8.50 (d, J=8.0 Hz, 1H).

$^{13}C$ NMR (DMSO-$d_6$) 14.05, 22.46, 60.82, 67.37, 169.19, 169.48 ppm.

IR (KBr) 3300, 1750, 1660, 1540, 1390, 610 $cm^{-1}$.

Mass spectrum (FD) 177 ($M^+$+1).

Elemental analysis Calculated for $C_6H_{12}N_2O_4$ 40.91% C; 6.87% H; 15.90% N. Found 40.79% C; 6.87% H; 15.90% N.

## EXAMPLE 47

Synthesis of Ethyl 2-Acetamido-2-(N-(N-methylhydroxyamino))acetate.

MeNHOH (17.39 mmol) (prepared from MeNHOH.HCl (2.00 g, 23.95 mmol) and NaOMe (0.94 g, 17.39 mmol)), and ethyl 2-bromo-2-acetamidoacetate (1.00 g, 4.46 mmol) gave an oily residue. The residue was triturated with EtOAc (5 mL) and the solid that remained was filtered and recrystallized from EtOH to give the desired product as a white solid.

Yield: 0.70 g (82%).

$R_f$ 0.34 (5% MeOH/$CHCl_3$).

mp 148°–150° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.17 (t, J=7.0 Hz, 3H), 1.89 (s, 3H), 2.37 (s, 3H), 4.00–4.20 (m, 2H), 5.04 (d, J=9.2 Hz, 1H), 8.17 (s, 1H), 8.43 (d, J=9.2 Hz, 1H).

$^{13}C$ NMR (DMSO-$d_6$) 14.04, 22.28, 43.78, 60.79, 71.46, 168.29, 170.23 ppm.

IR (KBr) 3320, 3200 (br), 1760, 1660, 1530, 1470, 720, 640 $cm^{-1}$.

Mass spectrum (FD) 192 ($M^+$+1).

Elemental analysis Calculated for $C_7H_{14}N_2O_4.0.25\ H_2O$ 43.18% C; 7.51% H; 14.39% N. Found 43.28% C; 7.25% H; 14.64% N.

## EXAMPLE 48

Synthesis of Ethyl 2-Acetamido-2-(N-(N,O-dimethylhydroxyamino))acetate.

MeNHOMe (17.40 mmol) (prepared from MeNHOMe.HCl (2.18 g, 22.32 mmol) and NaOMe (0.94 g, 17.40 mmol)) and ethyl 2-bromo-2-acetamidoacetate (1.00 g, 4.46 mmol) gave a residue which was purified by flash column chromatography on $SiO_2$ gel (1% MeOH/$CHCl_3$) to give the desired product as an oil.

Yield: 0.60 g (66%).

$R_f$ 0.53 (2% MeOH/$CHCl_3$).

$^1H$ NMR ($CDCl_3$) δ 1.35 (t, J=7.0 Hz, 3H), 2.12 (s, 3H), 2.62 (s, 3H), 3.46 (s, 3H), 4.30 (q, J=7.0 Hz, 2H), 5.36 (d, J=8.9 Hz, 1H), 6.66 (d, J=8.9 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$) 14.06, 22.89, 40.30, 60.01, 61.89, 70.16, 168.14, 170.53 ppm.

Synthesis of 2-Acetamido-N-benzyl-2-substituted Acetamides.

General Procedure.

A mixture of the ethyl 2-substituted-2-acetamidoacetate (1 equiv), benzylamine (1.2 equiv), and NaCN (0.1 equiv) in MeOH (1 mmol/25 mL) was stirred at 45°–50° C. (18 h). The solvent was removed in vacuo and the residue was purified using either trituration with EtOAc or flash column chromatography on $SiO_2$ gel with the indicated solvent as the eluent.

Using this procedure the following examples were prepared.

## EXAMPLE 49

Synthesis of 2-Acetamido-N-benzyl-2-aminoacetamide.

Ethyl 2-acetamido-2-aminoacetate (1.00 g, 6.25 mmol), benzylamine (0.80 g, 7.5 mmol) and NaCN (0.03 g, 0.61 mmol) gave a residue which solidified on standing (18 h). The reaction mixture was triturated with EtOAc (20 mL). The white solid which remained was filtered and then further purified by recrystallization from EtOAc.

Yield: 1.00 g (72%).

$R_f$ 0.21 (5% MeOH/$CHCl_3$).

mp 131°–133° C. (dec.).

$^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, 3H), 2.35 (br s, 2H), 4.28 (d, J=4.4 Hz, 2H), 4.91 (d, J=7.0 Hz, 1H), 7.20–7.32 (m, 5H), 8.31 (br s, 1H), 8.51 (br s, 1H).

$^{13}C$ NMR (DMSO-$d_6$) 22.6, 42.05, 60.29, 126.67, 127.10 (2 C), 128.18 (2 C), 139.23, 169.24, 170.67 ppm.

IR (KBr) 3300, 1650 (br), 1530 (br), 1450, 740 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 222 ($M^+$+100), 221 ($M^+$, 29), 133 (8).

Elemental analysis Calculated for $C_{11}H_{15}N_3O_2$ 59.71% C; 6.83% H; 18.99% N. Found 59.86% C; 6.88% H; 18.72% N.

## EXAMPLE 50

Synthesis of 2-Acetamido-N-benzyl-2-(methylamino) acetamide.

Ethyl 2-acetamido-2-(methylamino)acetate (1.50 g, 8.63 mmol), benzylamine (1.11 g, 10.35 mmol) and NaCN (0.04 g, 0.82 mmol) gave a brown residue which was purified by

flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to yield the desired product.

Yield: 1.00 g (49%).

$R_f$ 0.33 (3% MeOH/$CHCl_3$).

mp 115°–117° C. (recrystallized from ethyl acetate/petroleum ether).

$^1H$ NMR (DMSO-$d_6$) δ 1.87 (s, 3H), 2.18 (s, 3H), 4.20–4.29 (m, 2H), 4.87 (d, J=7.9 Hz, 1H), 7.24–7.35 (m, 5H), 8.14 (d, J=7.9 Hz, 1H), 8.55 (br s, 1H). The remaining amino proton was not detected.

$^{13}C$ NMR (DMSO-$d_6$) 22.52, 31.37, 42.04, 65.99, 126.68, 127.12 (2 C), 128.18 (2 C), 139.28, 169.51, 169.83 ppm.

IR (KBr) 3240, 1610 (br), 1500 (br), 1430, 725, 670 $cm^{-1}$.

Elemental analysis Calculated for $C_{12}H_{17}N_3O_2$ 61.26% C; 7.28% H; 17.86% N. Found 61.12% C; 7.01% H; 17.71% N.

## EXAMPLE 51

Synthesis of 2-Acetamido-N-benzyl-2-(ethylamino) acetamido.

Using ethyl 2-acetamido-2-(ethylamino)acetate (0.90 g, 4.79 mmol), benzylamine (0.62 g, 5.75 mmol), and NaCN (0.03 g, 0.51 mmol) gave an oily residue which was purified by flash column chromatography on $SiO_2$ gel (3% MeOH/$CHCl_3$) to give the desired product as a white solid.

Yield: 0.35 g (29%).

$R_f$ 0.34 (4% MeOH/$CHCl_3$).

mp 123°–125° C. (recrystallized from ethyl acetate/hexane).

$^1H$ NMR (DMSO-$d_6$) δ 0.93 (t, J=6.8 Hz, 3H), 1.81 (s, 3H), 2.08 (br s, 1H), 2.40–2.48 (m, 2H), 4.22 (d, J=5.5 Hz, 2H), 4.90 (d, J=7.8 Hz, 1H), 7.20–7.27 (m, 5H), 8.08 (d, J=7.8 Hz, 1H), 8.48 (t, J=5.5 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$) 15.14, 22.97, 37.65, 43.53, 65.68, 127.44 (2 C), 127.50, 128.64 (2 C), 137.73, 169.75, 171.20 ppm.

IR (KBr) 3250, 1620 (br), 1510 (br), 1450 (br), 740, 680 $cm^{-1}$.

Elemental analysis Calculated for $C_{13}H_{19}N_3O_2$ 62.63% C; 7.68% H; 16.85% N. Found 62.69% C; 7.49% H; 16.65% N.

## EXAMPLE 52

Synthesis of 2-Acetamido-N-benzyl-2-(N-anilino) acetamido.

Employing ethyl 2-acetamido-2-(N-anilino)acetate (2.00 g, 8.47 mmol), benzylamine (1.09 g, 10.00 mmol), and NaCN (0.04 g, 0.84 mmol) gave a white solid which separated during the course of the reaction. The precipitate was filtered and purified by recrystallization from absolute EtOH to give the desired product.

Yield: 1.10 g (44%).

mp 183°–185° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.84 (s, 3H), 4.31 (d, J=5.8 Hz, 2H), 5.67 (t, J=8.1 Hz, 1H), 6.04 (d, J=8.1 Hz, 1H), 6.59–6.64 (m, 1H), 6.70–6.72 (m, 2H), 7.06–7.11 (m, 2H), 7.20–7.33 (m, 5H), 8.41 (d, J=8.1 Hz, 1H), 8.72 (t, J=5.8 Hz, 1H).

$^{13}C$ NMR (DMSO-$d_6$) 22.46, 42.25, 60.42, 113.21 (2 C), 117.22, 126.72, 127.16 (2 C), 128.18 (2 C), 128.77 (2 C), 138.99, 145.88, 168.65, 169.70 ppm.

IR (KBr) 3270, 1630, 1520, 1490, 1430, 740, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 297 ($M^+$, 2), 239 (7), 164 (28), 163 (100), 122 (20), 121 (100), 106 (47), 104 (65), 93 (63), 91 (77).

Elemental analysis Calculated for $C_{17}H_{19}N_3O_2$ 68.67% C; 6.44% H; 14.13% N. Found 68.94% C; 6.42% H; 13.92% N.

## EXAMPLE 53

Synthesis of 2-Acetamido-N-benzyl-2-(N-(3-pyrazolylamino))acetamide.

A solution of ethyl 2-acetamido-2-(N-(3-pyrazolylamino)) acetate (1.60 g, 7.1 mmol) in MeOH (40 mL) containing benzylamine (0.83 g, 7.8 mmol) and NaCN (50 mg, 1 mmol) was stirred at 45–55° C. (18 h). TLC analysis (8% MeOH/$CHCl_3$) of the reaction mixture indicated the presence of only a minor amount of product. A second lot of NaCN (50 mg, 1 mmol) was then added and the reaction was allowed to proceed at 45°–55° C. (6 h) and then at room temperature (48 h). The solvent was removed in vacuo and the residue was triturated with EtOAc (15 mL). The insoluble solid that remained was filtered and purified by flash column chromatography on $SiO_2$ gel (7% MeOH/$CHCl_3$) to give the desired product.

Yield: 0.90 g (44%).

$R_f$ 0.35 (8% MeOH/$CHCl_3$).

mp 135°–137° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.82 (s, 3H), 4.29 (d, J=5.9 Hz, 2H), 5.51–5.55 (m, 3H), 7.18–7.40 (m, 6H), 8.36 (br s, 1H), 8.53 (br s, 1H), 11.66 (br s, 1H).

$^{13}C$. NMR (DMSO-$d_6$) 22.59, 42.29, 61.79, 90.68, 126.67, 127.07 (2 C), 128.17 (2 C), 129.10, 139.41, 153.53, 169.19, 169.67 ppm.

IR (KBr) 3230 (br), 1620 (br), 1500 (br), 1430, 730, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 288 ($M^+$+1, 64), 287 ($M^+$, 2), 230 (28), 229 (100), 153 (46).

Elemental analysis Calculated for $C_{14}H_{17}N_5O_2 \cdot 0.5\ H_2O$ 56.47% C; 6.12% H; 23.63% N. Found 56.63% C; 5.79% H; 23.43% N.

Preparation of Functionalized α-Heteroatom Substituted Amino Acids.

General Procedure.

A $BBr_3$ solution (1M in $CH_2Cl_2$, 1.1 equiv) was added to n solution of 2-acetamido-N-benzyl-2-ethoxyacetamido (1 equiv) in $CH_2Cl_2$ (10 mmol/125 mL). The mixture was stirred at room temperature (5 h) and then concentrated to dryness in vacuo to give 2-acetamido-N-benzyl-2-bromoacetamide as in pale yellow crystalline material. The bromo adduct was then dissolved in THF (10 mmol/250 mL), cooled (–78° C.), and then added over a 15 min interval to a cooled (–78° C.) solution of the heteroatom nucleophile in THF (1 mmol/1 mL). The reaction mixture was stirred at this temperature (30 min) and then at room temperature (90 min). The insoluble salts were filtered and the filtrate concentrated in vacuo. The residue was then purified by flash column chromatography on $SiO_2$ gel using the indicated solvent as the eluent.

Using this procedure the following examples were prepared.

## EXAMPLE 54

Synthesis of 2-Acetamido-N-benzyl-2-(N,N-dimethylamino)acetamido.

By making use of 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), $BBr_3$ (1M in $CH_2Cl_2$,

13.2 mL, 13.2 mmol), and $Me_2NH$ (5–6 equiv) was obtained a brown residue which was purified by flash column chromatography on $SiO_2$ gel (2.5% MeOH/$CHCl_3$) to give the desired product. The product was recrystallized from ethyl acetate/hexane to give light yellow cubic crystals.

Yield: 1.20 g (40%).

$R_f$ 0.39 (5% MeOH/$CHCl_3$).

mp 104°–106° C.

$^1$H NMR (DMSO-$d_6$) δ 1.91 (s, 3H), 2.11 (s, 6H), 4.22 (dd, J=5.2, 14.7 Hz, 1H), 4.34 (dd, J=6.1, 14.7 Hz, 1H), 5.11 (d, J=8.3 Hz, 1H), 7.23–7.31 (m, 5H), 8.18 (d, J=8.3 Hz, 1H), 8.55 (br s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.43, 40.33 (2 C), 42.28, 69.42, 126.73, 127.27 (2 C), 128.21(2 C), 139.49, 168.49, 170.31 ppm.

IR (KBr) 3280, 1670 (br), 1500 (br), 1460, 760, 700 $cm^{-1}$.

Mass spectrum 250 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{19}N_3O_2$ 62.63% C; 7.68% H; 16.85% N. Found 62.82% C; 7.66% H; 16.69% N.

## EXAMPLE 55

Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino) acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), $BBr_3$ (1M in $CH_2Cl_2$, 8.8 mL, 8.8 mmol), and anhydrous $NH_2OH$ (5–6 equiv) gave an oily residue. The residue was separated into three components by flash chromatography on $SiO_2$ gel (7.5% MeOH/$CHCl_3$).

2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.14 g (7%).

$R_f$ 0.30 (8% MeOH/$CHCl_3$).

mp 144°–146° C. (dec.) (recrystallized from EtOH)

$^1$H NMR (DMSO-$d_6$) δ 1.88 (s, 3H), 4.31 (d, J=5.7 Hz, 2H), 5.08 (dd, J=4.4, 8.1 Hz, 1H), 5.94 (dd, J=2.8, 4.4 Hz, 1H), 7.19–7.35 (m, 5H), 7.5 (d, J=2.8 Hz, 1H), 8.26 (d, J=8.1 Hz, 1H), 8.42 (t, J=5.7 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.69, 42.25, 67.86, 126.69, 127.14 (2 C), 128.18 (2 C), 139.08, 168.53, 169.67 ppm.

IR (KBr) 3320 (br), 1660 (br), 1540 (br), 1460, 750, 700 $cm^{-1}$.

Mass spectrum (FD) 238 ($M^+$+1).

Elemental analysis Calculated for $C_{11}H_{15}N_3O_3$ 55.69% C; 6.37% H; 17.71% N. Found 55.86% C; 6.37% H; 17.38% N.

Dimer A.

Yield: 0.05 g (3%).

$R_f$ 0.27 (8% MeOH/$CHCl_3$).

mp 177°–179° C. (recrystallized from EtOH).

$^1$H NMR (DMSO-$d_6$) δ 1.82 (s, 6H), 4.25–4.34 (m, 4H), 5.21 (d, J=9.3 Hz, 2H) 7.20–73.3 (m, 10H), 8.16 (d, J=9.3 Hz, 2H), 8.26 (t, J=5.8 Hz, 2H), 8.51 (s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.54 (2 C), 42.30 (2 C), 67.55 (2 C), 126.63 (2 C), 127.13 (4 C), 128.11 (4 C), 139.02 (2 C), 168.24 (2 C), 169.33 (2 C) ppm.

IR (KBr) 3240 (br), 1640 (br), 1510 (br), 1450, 690 $cm^{-1}$.

Mass spectrum (FD) 442 ($M^+$+1).

Elemental analysis Calculated for $C_{22}H_{27}N_5O_5$ 59.85% C; 6.16% H; 15.86% N. Found 59.56% C; 6.08% H; 15.64% N.

Dimer B.

Yield: 0.10 g (6%).

$R_f$ 0.18 (8% MeOH/$CHCl_3$).

mp 184°–186° C. (recrystallized from MeOH).

$^1$H NMR (DMSO-$d_6$) δ 1.87 (6H), 4.20 (dd, J=5.3, 15.3 Hz, 2H), 4.44 (dd, J=6.2, 15.3 Hz, 2H), 5.28 (d, J=9.0 Hz, 2H), 7.15–7.31 (m, 10H), 8.00 (d, J=9.0 Hz, 2H), 8.39 (dd, J=5.3, 6.2 Hz, 2H), 8.51 (s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.50 (2 C), 42.58 (2 C), 69.98 (2 C), 126.73 (2 C), 127.23 (4 C), 128.22 (4 C), 139.08 (2 C), 167.60 (2 C), 169.57 (2 C) ppm.

IR (KBr) 3300 (br), 1660 (br), 1530 (br), 1450, 740, 700 $cm^{-1}$.

Mass spectrum (FD) 442 ($M^+$+1).

Elemental analysis Calculated for $C_{22}H_{27}N_5O_5$ 59.85% C; 6.16% H; 15.86% N. Found 60.09% C; 5.93% H; 15.76% N.

## EXAMPLE 56

Improved Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

2-Acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol) and $BBr_3$ (1M in $CH_2Cl_2$, 17.2 mL, 17.2 mmol)) was dissolved in THF (250 mL), cooled (−10° C.), and then added dropwise (30 min) to a suspension of $NH_2OH$ (5–6 equiv) in THF (50 mL) at −10° C. The reaction mixture was stirred (30 min) at this temperature and then allowed to warm to room temperature (1 h). The insoluble materials were filtered and the filtrate was concentrated in vacuo. The residue was separated into two components by flash column chromatography on $SiO_2$ gel (7.5% MeOH/$CHCl_3$).

2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.66 g (23%).

mp 144°–146° C. (dec.) (recrystallized from EtOH).

Dimer B.

Yield: 0.10 g (5%).

mp 184°–186° C. (recrystallized from MeOH).

Dimer A was not observed under these conditions.

## EXAMPLE 57

Synthesis of 2-Acetamido-N-benzyl-2-($N^2$-phenylhydrazino)acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), $BBr_3$ (1M in $CH_2Cl_2$, 10.0 mL, 10.0 mmol), and phenylhydrazine (2.60 g, 24.0 mmol) gave a pale yellow oily residue which was purified by flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give the desired product. The product was recrystallized from chloroform/hexane as a light yellow solid.

Yield: 0.75 g (29%).

$R_f$ 0.26 (2% MeOH/$CHCl_3$).

mp 132°–134° C.

$^1$H NMR (DMSO-$d_6$) δ 1.89 (s, 3H), 4.28 (d, J=5.8 Hz, 2H), 4.89 (d, J=5.2 Hz, 1H), 5.09 (dd, J=5.2, 7.4 Hz, 1H), 6.61 (t, J=7.4 Hz, 1H), 6.70–7.28 (m, 10H), 8.29 (d, J=7.4 Hz, 1H), 8.60 (t, J=5.8 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.88, 42.22, 66.22, 112.66 (2 C), 117.57, 126.65, 127.08 (2 C), 128.15 (2 C), 128.53 (2 C), 139.12, 149.90, 168.66, 170.04 ppm.

IR (KBr) 3300, 1640 (br), 1610, 1520 (br), 1460, 760, 700 $cm^{-1}$.

Mass spectra (FD) 313 ($M^+$+1).

Elemental analysis Calculated for $C_{17}H_{20}N_4O_2$ 65.37% C; 6.45% H; 17.94% N. Found 65.15% C; 6.25% H; 17.71% N.

## EXAMPLE 58

Synthesis of 2-Acetamido-N-benzyl-2-($N^2$-benzyloxycarbonylhydrazino)acetamide.

Employing 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), $BBr_3$ (1M in $CH_2Cl_2$, 15.0 mL, 15.0 mmol), and benzyl carbazate (4.58 g, 27.6 mmol), 0.95 g (21%) of the desired product was obtained. The product was recrystallized from chloroform/hexane to give a white amorphous solid.

$R_f$ 0.32 (2% MeOH/$CHCl_3$).

mp 152°–154° C.

$^1$H NMR (DMSO-$d_6$) δ 1.85 (s, 3H), 4.27 (d, J=4.4 Hz, 2H), 5.00 (s, 2H), 5.14 (dd,J=3.1, 8.0 Hz, 1H), 5.23 (t, J=3.1 Hz, 1H), 7.25–7.35 (m, 10H), 8.26 (d, J=8.0 Hz, 1H), 8.56 (br s, 1H), 8.66 (br s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.71, 42.23, 65.56, 65.97, 126.69, 127.16 (2 C), 127.61 (2 C), 127.77, 128.13 (2 C), 128.27 (2 C), 136.74, 138.87, 168.04, 169.95 ppm.

IR (KBr) 3325, 1620 (br), 1500 (br), 1440, 740, 680 $cm^{-1}$.

Mass spectrum (FD) 371 ($M^+$+1).

Elemental analysis Calculated for $C_{19}H_{22}N_4O_4$ 61.61% C; 5.99% H; 15.13% N. Found 61.40% C; 6.21% H; 15.39% N.

## EXAMPLE 59

Synthesis of 2-Acetamido-N-benzyl-2-phenoxyacetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), $BBr_3$ (1M in $CH_2Cl_2$, 15.0 mL, 15.0 mmol), and NaOPh (4.18 g, 30 mmol) gave a brown oily residue which was purified by flash column chromatography on $SiO_2$ gel using first $CHCl_3$ and then 2% MeOH/$CHCl_3$ as the eluents to give the desired product. The compound was recrystallized from chloroform/hexane.

Yield: 0.80 g (22%).

$R_f$ 0.58 (3% MeOH/$CHCl_3$).

mp 125°–128° C. (softens at 122° C.).

$^1$H NMR (DMSO-$d_6$) δ 1.83 (s, 3H), 4.35 (d, J=5.7 Hz, 2H), 6.18 (d, J=9.4 Hz, 1H), 6.94–6.99 (m, 2H), 7.02–7.33 (m, 8H), 8.98 (t, J=5.7 Hz, 1H), 9.10 (d, J=9.4 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.54, 42.24, 76.44, 116.09 (2 C), 121.78, 126.84, 127.26 (2 C), 128.25 (2 C), 128.44 (2 C), 138.84, 155.97, 166.63, 170.73 ppm.

IR (KBr) 3300, 1650 (br), 1600, 1530 (br), 1490, 1450, 760, 700 $cm^{-1}$.

Mass spectrum (FD) 299 ($M^+$+1).

Elemental analysis Calculated for $C_{17}H_{18}N_2O_3.0.5\ H_2O$ 66.43% C; 6.23% H; 9.11% N. Found 66.62% C; 6.23% H; 9.16% N.

## EXAMPLE 60

Synthesis of 2-Acetamido-N-benzyl-2-(methylmercapto) acetamide.

A cooled (–78° C.) solution or $Et_3N$ (4.85 g, 48.0 mmol) in THF (20 mL) was added to a cooled (–78° C.) solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and $BBr_3$ (1M in $CH_2Cl_2$, 20.0 mL, 20.0 mmol)) in THF (275 mL). A cooled (–78° C.) solution of excess MeSH (5–6 equiv) in THF (55 mL) was then added. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (1 h). The insoluble materials were filtered and the filtrate was evaporated to dryness in vacuo. The oily residue obtained was purified by flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give 1.10 g (27%) of the desired product as a yellow orange oil. The product was purified by a second flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give 0.72 g of the pure product as a white solid.

$R_f$ 0.65 (3% MeOH/$CHCl_3$).

mp 155°–157° C.

$^1$H NMR ($CD_3NO_2$) δ 1.98 (s, 3H), 2.08 (s, 3H), 4.39 (dd, J=6.1, 15.2 Hz, 1H), 4.49 (dd, J=6.1, 15.2 Hz, 1H), 5.51 (d, J=7.8 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H), 7.17–7.41 (m, 6H).

$^{13}$C NMR ($CD_3NO_2$) 12.28, 22.94, 44.26, 56.03, 128.46, 128.60 (2 C), 129.77 (2 C), 140.17, 169.19, 171.06 ppm.

IR (KBr) 3320, 1650 (br), 1520 (br), 1460, 750 $cm^{-1}$.

Mass spectrum (FD) 253 ($M^+$+1).

Elemental analysis Calculated for $C_{12}H_{16}N_2O_2S$ 57.12% C; 6.39% H; 11.10% N. Found 57.06% C; 6.57% H; 11.28% N.

## EXAMPLE 61

Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto) acetamide.

Using the procedure described for the synthesis of 2-acetamido-N-benzyl-2-(methylmercapto)acetamide, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and EtSH (0.65 g, 10.4 mmol) were converted to 0.80 g (38%) of the desired product. The compound was further purified by recrystallization from chloroform/hexane to give a beige solid.

$R_f$ 0.60 (4% MeOH/$CHCl_3$).

mp 146°–148° C.

$^1$H NMR (DMSO-$d_6$) δ 1.56 (t, J=7.4 Hz, 3H), 1.88 (s, 3H), 2.49–2.67 (m, 2H), 4.23 (dd, J=5.9, 15.2 Hz, 1H), 4.32 (dd, J=5.9, 15.2 Hz, 1H), 5.55 (d, J=9.1 Hz, 1H), 7.20–7.35 (m, 5H), 8.59 (d, J=9.1 Hz, 1H), 8.75 (t, J=5.9 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 14.73, 22.43, 23.73, 42.10, 53.70, 126.87, 127.14 (2 C), 128.32 (2 C), 139.01, 167.89, 169.02 ppm.

IR (KBr) 3240, 1620 (br), 1510 (br), 1415, 680, 640 $cm^{-1}$.

Mass spectrum (FD) 267 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{18}N_2O_2S.0.25\ H_2O$ 57.65% C; 6.88% H; 10.34% N. Found 57.48% C; 6.84% H; 10.28% N.

Preparation of Functionalized α-Heteroatom Substituted Amino Acids.

General Procedure.

A mixture of 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (1 eqiuv), and the nitrogen nucleophile (4–5 equiv) in MeOH (1 mmol/1 mL) was stirred at 55°–60° C. (3 h). The solvent was removed in vacuo and the residue was purified by flash column chromatography on $SiO_2$ gel using the indicated solvents as the eluent.

Using this procedure the following examples were prepared.

## EXAMPLE 62

Synthesis of 2-Acetamido-N-benzyl-2-(N-methoxyamino) acetamide.

Using a MeOH solution of $MeONH_2$ (prepared from $MeONH_2$.HCl (2.83 g, 33.9 mmol) and NaOMe (1.41 g, 26.1 mmol)), and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.70 g, 7.67 mmol) gave an oily residue which was purified by flash column chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give the desired product. The product was recrystallized from chloroform/hexane.

Yield: 0.80 g (42%).

$R_f$ 0.23 (2% MeOH/$CHCl_3$)

mp 95°–97° C.

$^1$H NMR (DMSO-$d_6$) δ 1.88 (s, 3H), 3.38 (s, 3H), 4.22–4.41 (m, 2H), 5.18 (dd, J=4.9, 7.8 Hz, 1H), 6.78 (d, J=4.9 Hz, 1H), 7.21–7.32 (m, 5H), 8.33 (d, J=7.8 Hz, 1H), 8.56 (br s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.64, 42.28, 61.42, 66.25, 126.74, 127.19 (2 C), 128.19 (2 C), 139.11, 167.95, 169.66 ppm.

IR (KBr) 3300, 1650, 1620, 1510 (br), 1440, 750, 680 $cm^{-1}$.

Mass spectrum (FD) 252 ($M^+$+1).

Elemental analysis Calculated for $C_{12}H_{17}N_3O_3$ 57.63% C; 6.82% H; 16.72% N. Found 57.06% C; 6.63% H; 16.65% N.

## EXAMPLE 63

Synthesis of 2-Acetamido-N-benzyl-2-(N-(N-methylhydroxyamino))acetamide.

An MeOH solution (30 mL) of MeNHOH (21.74 mmol) (prepared from MeNHOH.HCl (2.36 g, 28.26 mmol) and NaOMe (1.17 g, 21.74 mmol)) and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.20 g, 6.25 mmol) gave a residue which was purified by flash column chromatography on $SiO_2$ gel (6% MeOH/$CHCl_3$) to give the desired product as a white solid. The product was then purified by recrystallization from EtOH.

Yield: 0.95 g (61%).

$R_f$ 0.32 (8% MeOH/$CHCl_3$).

mp 159°–161° C.

$^1$H NMR (DMSO-$d_6$) δ 1.95 (s, 3H), 2.43 (s, 3H), 4.26 (dd, J=5.7, 15.1 Hz, 1H), 4.35 (dd, J=5.7, 1.51 Hz, 1H), 5.09 (d, J=9.1 Hz, 1H), 7.21–7.29 (m, 5H), 8.05 (s, 1H), 8.18 (d, J=9.1 Hz, 1H), 8.23 (t, J=5.7 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.40, 42.34, 43.92, 71.49, 126.62, 127.12 (2 C), 128.12 (2 C), 139.14, 167.82, 170.28 ppm.

IR (KBr) 3440 (br), 3300, 1640, 1530, 1460, 750, 700 $cm^{-1}$.

Mass spectrum (FD) 252 ($M^+$+1).

Elemental analysis Calculated for $C_{12}H_{17}N_3O_3$ 57.36% C; 6.82% H; 16.72% N. Found 57.65% C; 6.59% H; 16.66% N.

## EXAMPLE 64

Synthesis of 2-Acetamido-N-benzyl-2-(N-(N,O-methylhydroxyamino))acetamide.

An MeOH solution (20 mL) of MeNHOMe (17.39 mmol) (prepared from MeNHOMe.HCl (2.20 g, 23.02 mmol) and NaOMe (0.94 g, 17.39 mmol)) and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.10 g, 5.97 mmol) gave a solid residue. Flash column chromatography of the solid on $SiO_2$ gel (2% MeOH/$CHCl_3$) yielded pure desired product. The product was recrystallized from EtOH.

Yield: 1.30 g (82%).

$R_f$ 0.39 (2% MeOH/$CHCl_3$).

mp 165°–167° C.

$^1$H NMR (DMSO-$d_6$) δ 1.93 (s, 3H), 2.43 (s, 3H), 3.32 (s, 3H), 4.25 (dd, J=5.9, 149 Hz, 1H), 4.37 (dd, J=5.9, 14.9 Hz, 1H), 5.19 (d, J=9.4 Hz, 1H), 7.21–7.35 (m, 5H), 8.31 (d, J=9.4 Hz, 1H), 8.56 (t, J=5.9 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.36, 39.68, 42.34, 59.16, 70.33, 126.74, 127.41 (2 C), 128.21 (2 C), 139.30, 167.38, 170.30 ppm.

IR (KBr) 3300, 1640 (br), 1540 (br), 1460, 750, 700 $cm^{-1}$.

Mass spectrum (FD) 266 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{19}N_3O_3$ 58.85% C; 7.22% H; 15.84% N. Found 59.05% C; 7.37% H; 15.75% N.

## EXAMPLE 65

Synthesis of 2-Acetamido-N-benzyl-2-(N-isoxazolidino) acetamide.

Using 2-acetamido-2-(N,N,N-trimethylammonium) acetamide tetrafluoroborate (1.60 g, 4.55 mmol), isoxazolidine (prepared from isoxazolidine hydrobromide (2.41 g, 15.65 mmol) and NaOMe (0.70 g, 13.04 mmol)) gave the desired product. The product was recrystallized from chloroform/hexane to give a white amorphous solid.

Yield: 0.80 g (64%).

$R_f$ 0.29 (4% MeOH/$CHCl_3$).

mp 149°–151° C.

$^1$H NMR (DMSO-$d_6$) δ 1.91 (s, 3H), 2.05–2.20 (m, 2H), 2.45–2.89 (m, 1H), 2.98–3.07 (m, 1H), 3.74–3.90 (m, 2H), 4.25 (dd, J=6.1, 15.3 Hz, 1H), 4.35 (dd, J=6.1, 15.3 Hz, 1H), 5.23 (d, J=9.2 Hz, 1H), 7.15–7.35 (m, 5H), 8.49 (d, J=9.2 Hz, 1H), 8.56 (br s, 1H).

$^{13}$C NMR (DMSO-$d_6$) 22.26, 28.26, 42.15, 48.94, 66.19, 68.77, 126.64, 127.02 (2 C), 128.13 (2 C), 139.22, 167.43, 170.27 ppm.

IR (KBr) 3400 (br), 3300, 1650, 1530, 1470, 740, 700, 610 $cm^{-1}$.

Mass Spectrum (FD) 278 ($M^+$+1).

Elemental analysis Calculated for $C_{14}H_{19}N_3O_3$ 60.64% C; 6.91% H; 15.15% N. Found 60.16% C; 7.04% H; 15.07% N.

Preparation of Functionalized α-Heteroatom Substituted Amino Acids.

General Procedure.

2-Acetamido-N-benzyl-2-ethoxyacetamide (1 equiv) was suspended in $Et_2O$ (100 mL/100 mmol), and then $BF_3.Et_2O$ (1.6–2.4 equiv) was rapidly added and the resulting solution was stirred (10 min). The nucleophile ($H_2O$ or EtSH) (1.6–4.0 equiv) was then added and the reaction was stirred at room temperature (18–48 h). The reaction was then quenched by the addition of an aqueous $NaHCO_3$ (100 mL/10 mmol)/ice mixture. The experimental workup varied slightly for each compound and is described in the following examples along with the observed spectral properties.

## EXAMPLE 66

Synthesis of 2-Acetamido-N-benzyl-2-hydroxyacetamide.

Reacting 2-acetamido-N-benzyl-2-ethoxyacetamide (1.00 g, 4.0 mmol), $BF_3.Et_2O$ (0.91 g, 6.4 mmol) and $H_2O$ (0.12 g, 6.7 mmol) followed by aqueous $NaHCO_3$ workup gave an aqueous reaction mixture. The solution was then extracted with EtOAc (3×50 mL), and the combined EtOAc extracts were dried ($Na_2SO_4$), and concentrated in vacuo. The resi-

due was purified by flash column chromatography on $SiO_2$ gel (3% MeOH/$CHCl_3$) to give the desired product as a white solid.

Yield: 0.30 g (34%).

$R_f$ 0.14 (3% MeOH/$CHCl_3$).

mp 136°–138° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, 3H), 4.29 (d, J=5.9 Hz, 2H), 5.48 (dd, J=5.5, 8.6 Hz, 1H), 6.47 (d, J=5.5 Hz, 1H), 7.21–7.35 (m, 5H), 8.52 (t, J=5.9 Hz, 1H), 8.59 (d, J=8.6 Hz, 1H).

$^{13}C$ NMR (DMSO-$d_6$) 22.66, 41.99, 71.42, 126.66, 127.22 (2 C), 128.13 (2 C), 139.20, 169.47, 169.62 ppm.

IR (KBr) 3300, 1620, 1530 (br), 1430 (br), 730, 690 $cm^{-1}$.

Mass spectrum, m/e (relative intensity) 223 ($M^+$+1, 1), 163 (11), 134 (9), 106 (46), 91 (100), 77 (22), 65 (38).

Elemental analysis Calculated for $C_{11}H_{14}N_2O_3$ 59.45% C; 6.35% H; 12.61% N. Found 59.24% C; 6.36% H; 12.50% N.

## EXAMPLE 67

Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto) acetamido.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), $BF_3.Et_2O$ (2.72 g, 19.2 mmol) and EtSH (2.38 g, 38.4 mmol) gave an aqueous reaction mixture. The solution was extracted with $CHCl_3$ (3×100 mL). The combined $CHCl_3$ layers were dried ($Na_2SO_4$), and then concentrated in vacuo to give the desired product as white solid.

Yield: 1.90 g (89%).

$R_f$ 0.60 (4% MeOH/$CHCl_3$).

mp 148°–149° C. (mixed melting point with an authentic sample, of Example 61 was undepressed).

## EXAMPLE 68

Synthesis of 2,2-Dicacetamido-N-benzylacetamide.

$Ac_2O$ (1 mL) was added to a solution of 2-acetamido-N-benzyl-2-aminoacetamide (1.10 g, 4.98 mmol) in dry pyridine (10 mL) and then $CH_2Cl_2$ (20 mL) was added. The mixture was stirred at room temperature (4 h) and then the volatile materials were removed in vacuo. The residue was then treated with a saturated aqueous $NaHCO_3$ solution (50 mL). The white solid that remained was the desired product and-was filtered, dried ($Na_2SO_4$), and recrystallized from MeOH.

Yield: 1.20 g (92%).

mp 265°–267° C. (dec.).

$^1H$ NMR (DMSO-$d_6$) δ 1.84 (s, 6H), 4.26 (d, J=5.8 Hz, 2H), 5.71 (t, J=7.6 Hz, 1H), 7.20–7.31 (m, 5H), 8.44 (d, J=7.6 Hz, 2H), 8.48 (t, J=5.8 Hz, 1H).

$^{13}C$ (DMSO-$d_6$) 22.44 (2 C), 42.26, 56.99, 126.62, 127.02 (2 C), 128.12 (2 C), 139.15, 168.19, 169.39 (2 C) ppm.

IR (KBr) 3260, 1530, 1500, 740, 690 $cm^{-1}$.

Mass spectrum (FD) 264 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{17}N_3O_3$ 59.30% C; 6.51% H; 15.96% N. 59.16% C; 6.49% H; 15.86% N.

## EXAMPLE 69

Synthesis of 2-Acetamido-N-benzyl-2-trifluoroacetamidoacetamide.

Ice cold trifluoroacetic anhydride (8 mL) was added in one portion to ice cold 2-acetamido-N-benzyl-2-aminoacetamide (1.00 g, 4.53 mmol). The reaction was accompanied by the evolution of heat. After stirring (5 min), the volatile materials were removed in vacuo. The residue was treated with a saturated aqueous $NaHCO_3$ solution (20 mL), and the solid that remained was filtered and washed with $H_2O$ to give the desired product. The product was recrystallized from EtOH.

Yield: 1.00 g (70%).

$R_f$ 0.34 (8% MeOH/$CHCl_3$).

mp 228°–230° C.

$^1H$ NMR (DMSO-$d_6$) δ 1.90 (s, 3H), 4.30 (d, J=5.1 Hz, 2H), 5.85 (d, J=8.0 Hz, 1H), 7.21–7.35 (m, 5H), 8.64 (d, J=8.0 Hz, 1H), 8.75 (t, J=5.1 Hz, 1H), 10.04 (s, 1H).

$^{13}C$ NMR(DMSO-$d_6$) 22.52, 42.52, 57.42, 117.4 (q, JCF= 288.3 Hz), 126.80, 127.16 (2 C), 128.21 (2 C), 138.93, 156.14 (q, JCF=35.3 Hz), 166.3.9, 169.88 ppm.

IR (KBr) 3300, 1720, 1660, 1520, 1380, 760, 700 $cm^{-1}$.

Mass spectrum (FD) 318 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{14}N_3O_3F_3$ 49.21% C; 4.45% H; 13.24% N. Found 49.48% C; 4.43% H; 13.10% N.

## EXAMPLE 70

Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide Tetrafluoroborate.

A solution of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitromethane (6 mL). The reaction mixture was stirred at this temperature (15 min) and then at room temperature (2 h). Anhydrous $Et_2O$ (~50 mL) was added the reaction mixture and the white solid that separated was filtered, washed with $Et_2O$, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171°–173° C. (dec.).

$^1H$ NMR ($CD_3NO_2$) δ 2.14 (s, 3H), 3.18 (s, 9H), 4.50 (d, J=5.8 Hz, 2H), 5.70 (d, J=9.3 Hz, 1H), 7.30–7.41 (m, 5H), 7.57 (d, J=9.3 Hz, 1H), 7.70 (br s, 1H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 $cm^{-1}$.

Mass spectrum (FD) 264 ($M^+$).

Elemental analysis Calculated for $C_{14}H_{22}N_3O_2BF_4$ 47.89% C; 6.31% H; 11.97% N. Found 47.80% C; 6.33% H; 12.00% N.

## EXAMPLE 71

Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto) acetamide-S-oxide.

A solution of m-chloroperbenzoic acid (1.00 g (~65%), 3.76 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise into a stirred, cooled (−10° to −15° C.) $CH_2Cl_2$ solution (125 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (1.00 g, 3.76 mmol) under $N_2$. The reaction was stirred (30 min) at this temperature and then, the m-chlorobenzoic acid was precipitated as its ammonium salt by passing $NH_3$ gas over the surface of the reaction solution. The excess $NH_3$ was removed by passing $N_2$ gas through the solution (20 min) at room temperature. The ammonium salt was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on $SiO_2$ gel (2% MeOH/$CHCl_3$) to give the desired product. The product was recrystallized from chloroform/hexane as a white granular solid.

Yield: 0.55 g (52%).

$R_f$ 0.23 (2% MeOH/$CHCl_3$).

mp 135°–137° C.

$^1$H NMR (DMSO-$d_6$) δ 1.15 (t, J=7.5 Hz, 3H), 1.99 (s, 3H), 2.49–2.56 (m, 1H), 2.65–2.72 (m, 1H), 4.34 (d, J=5.7 Hz, 2H), 5.55 (d, J=9.5 Hz, 1H), 7.23–7.34 (m, 5H), 8.74 (d, J=9.5 Hz, 1H), 8.77 (t, J=5.7 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 7.03, 22.34, 42.40, 42.47, 67.15, 126.89, 127.27 (2 C), 128.24 (2 C), 138.55, 164.66, 170.18 ppm.

IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm$^{-1}$.

Mass spectrum (FD) 283 ($M^+$+1).

Elemental analysis Calculated for $C_{13}H_{18}N_2O_3S$ 55.30% C; 6.43% H; 9.92% N. Found 55.17% C; 6.38% H; 9.70% N.

## EXAMPLE 72

Synthesis of 2-Acetamido-N-benzyl-2-(S-ethylmercapto) acetamide-S-oxide.

A solution of $NaIO_4$ (1.77 g, 8.27 mmol) in $H_2O$ (20 mL) was added dropwise into a stirred solution of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (2.00 g, 7.52 mmol) in MeOH (25 mL). A precipitate appeared rapidly. $H_2O$ (~30 mL) was added to the mixture to dissolve most of the suspension, and the reaction was stirred (4 h) at room temperature. The reaction was concentrated in vacuo and the remaining aqueous mixture was extracted with $CHCl_3$ (3×100 mL). The combined $CHCl_3$ extracts were dried ($Na_2SO_4$) and the solvent was removed in vacuo. The oily residue (1.95 g, 92%) solidified on drying in vacuo. NMR analysis (DMSO-$d_6$) or the product showed that it was a 2:1 mixture of the two diastereomers of the desired product. The reaction was recrystallized from EtOAc to give nearly pure diastereomer A (1.20 g) that was obtained from the m-chloroperbenzoic acid reaction. The EtOAc mother liquor was concentrated and the remaining residue (0.75 g) was recrystallized from ethyl acetate/hexane to give a diastereomeric mixture (0.41 g) of the two diastereomers A and B in a 2:3 ratio, respectively.

$R_f$ 0.60 (4% MeOH/$CHCl_3$).

mp 135°–137° C. (softens at 117° C.).

IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm$^{-1}$.

Mass spectrum (FD) 283 ($M^+$+1).

Elemental analysis: Calculated for $C_{13}H_{18}N_2O_3S$: 55.30% C; 6.43% H; 9.92% N. Found: 55.58% C; 6.49% H; 9.97% N.

The following NMR spectral properties have been assigned to compounds A and B.

Diastereomer A.

$^1$H NMR (DMSO-$d_6$) δ 1.16 (t, J=7.5 Hz, 3H), 2.00 (s, 3H), 2.49–2.72 (m, 2H), 4.28–4.39 (m, 2H), 5.56 (d, J=9.7 Hz, 1H), 7.21–7.34 (m, 5H), 8.71–8.77 (m, 2H).

$^{13}$C NMR (DMSO-$d_6$) 7.10, 22.43, 42.48, 42.57, 67.23, 126.98, 127.36 (2 C), 128.33 (2 C), 138.63, 164.73, 170.25 ppm.

Diastereomer B.

$^1$H NMR (DMSO-$d_6$) δ 1.13 (t, J=7.6 Hz, 3H), 1.94 (s, 3H), 2.49–2.72 (m, 2H), 4.28–4.39 (m, 2H), 5.71 (d, J=9.9 Hz, 1H), 7.21–7.34 (m, 5H), 8.83 (d, J=9.9 Hz, 1H), 8.98 (t, J=5.6 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 6.47, 22.43, 41.53, 42.55, 67.90, 126.98, 127.36 (2 C), 128.33 (2 C), 138.39, 164.43, 169.82 ppm.

## EXAMPLE 73

Synthesis of 2-Acetamido-N-benzyl-2-(ethanesulfonyl) acetamide.

An aqueous solution (20 mL) of $NaIO_4$ (3.00 g, 14.02 mmol) was added to a MeOH solution (20 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (0.95 g, 3.57 mmol). The initial homogeneous solution rapidly became turbid. $H_2O$ (~10 mL) was then added dropwise until the system became homogeneous. The solution was stirred (18 h) at 50°–60° C. MeOH (50 mL) was added to the reaction solution and the precipitated salt was filtered and washed with MeOH (10 mL). The filtrate was concentrated and the remaining solution was extracted with $CHCl_3$ (3×50 mL). The combined $CHCl_3$ extracts were dried ($Na_2SO_4$), and concentrated in vacuo. Time residue was purified by flash chromatography on $SiO_2$ gel (1% MeOH/$CHCl_3$) to give the desired product. The product was further purified by recrystallization from EtOH:.

Yield: 0.34 g (32%).

$R_f$ 0.34 (3% MeOH/$CHCl_3$).

mp 161°–163° C.

$^1$H NMR (DMSO-$d_6$) δ 1.22 (t, J=7.4 Hz, 3H), 1.99 (s, 3H), 3.04–3.24 (m, 2H), 4.31 (dd, J=5.7, 15.3 Hz, 1H), 4.41 (dd, J=5.7, 15.3 Hz, 1H), 5.93 (d, J=9.8 Hz, 1H), 7.22–7.35 (m, 5H), 9.13 (t, J=5.7 Hz, 1H), 9.17 (d, J=9.8 Hz, 1H).

$^{13}$C NMR (DMSO-$d_6$) 5.72, 22.27, 42.63, 45.43, 69.14, 127.02, 127.28 (2 C), 128.33 (2 C), 138.16, 161.88, 169.83 ppm.

IR (KBr) 3300, 2940, 1660, 1520, 1310, 1230, 1120, 900 cm$^{-1}$.

Mass spectrum (FD) 298 ($M^+$).

Elemental analysis Calculated for $C_{13}H_{18}N_2O_4S$ 52.33% C; 6.08% H; 9.39% N. Found 52.52% C; 6.06% H; 9.53% N.

## EXAMPLE 74

Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide Tetrafluoroborate.

A solution or 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitromethane (6 mL). The reaction mixture was stirred at this temperature (15 min) and then at room temperature (2 h). Anhydrous $Et_2O$ (~50 mL) was added to the reaction mixture and the white solid that separated was filtered, washed with $Et_2O$, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171°–173° C. (dec.).

$^1$H NMR ($CD_3NO_2$) δ 2.14 (s, 3H), 3.18 (s, 9H), 4.50 (d, J=5.8 Hz, 2H), 5.70 (d, J=9.3 Hz, 1H), 7.30–7.41 (m, 5H), 7.57 (d, J=9.3 Hz, 1H), 7.70 (br s, 1H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm$^{-1}$.

Mass spectrum (FD) 264 ($M^+$).

Elemental analysis

Calculated for $C_{14}H_{22}N_3O_2BF_4$ 47.89% C; 6.31% H; 11.97% N. Found 47.80% C; 6.33% H; 12.00% N.

## EXAMPLE 75

Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole) acetamide.

A solution 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide

(2.00 g, 8.0 mmol) and $BBr_3$ (1M $CH_2Cl_2$ solution, 8.8 mL, 8.8 mmol)) was prepared in THF (225 mL) and cooled to −78° C. It was then added under $N_2$ gas atmosphere to a cooled (−78° C.) suspension of potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was stirred at −78° C. (1 h) and then at room temperature (1 h). H was then treated with water (10 mL) and acidified with 5% citric acid to pH 4.0 after which it was made basic with aqueous saturated $Na_2CO_3$ solution. The aqueous mixture was extracted with EtOAc (2×250 mL) and the organic layers were dried ($Na_2SO_4$). The volatile materials were removed in vacuo and the residue was purified by flash column chromatography on silica gel using 3% MeOH/$CHCl_3$ as the eluant to give 0.4 g (18%) of the desired product. It was purified by recrystallization from EtOH: mp 182°–184° C.; $R_f$ 0.44 (4% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.91 (s, $COCH_3$), 4.30 (d, J=5.5 Hz, $CH_2$), 6.01 (s, 2×$C_3H$), 6.38 (d, J=8.7 Hz, CH), 6.85 (s, 2×$C_2H$), 7.11–7.35 (m, 5PhH), 8.96 (t, J=5.5 Hz, NH), 9.14 (d, J=8.7 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.22 ($COCH_3$), 42.15 ($CH_2$), 62.86 (CH), 107.79 ($2C_3$), 119.19 ($2C_2$), 126.76 ($C_{4'}$), 127.01 ($2C_{2'}$ or $2C_{3'}$), 128.11 ($2C_{2'}$ or $2C_{3'}$), 138.34 ($C_{1'}$), 166.37 (CONH), 169.41 ($COCH_3$) ppm; mass spectrum, m/e (relative intensity) 272 ($M^+$+1, 22), 271 ($M^+$, 100).

Anal. Calcd for $C_{15}H_{17}N_3O_2.0.2\ H_2O$: C, 65.53; H, 6.37; N, 15.28. Found: C, 65.80; H, 6.22; N, 15.13.

## EXAMPLE 76

Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole) acetamide.

Making use of the experimental procedure described in the above experiment, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 8.8 mL, 8.8 mmol), $Et_3N$ (1.62 g, 1.60 mmol), and imidazole (0.60 g, 8.8 mmol) gave 0.60 g (30%) of the desired product. It was recrystallized from ethyl acetate/hexane as a beige colored solid: mp 146°–148° C.; $R_f$0. (7% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, $COCH_3$), 4.30 (br s, $CH_2$), 6.53 (d, J=8.0 Hz, CH), 6.89 (s, $C_5H$), 7.12–7.33 (m, $C_4H$, 5PhH), 7.69 (s, $C_2H$), 9.06 (br s, NH), 9.29 (d, J=8.0 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.28 ($COCH_3$), 42.36 ($CH_2$), 61.18 (CH), 117.56 ($C_5$), 126.92 ($C_{4'}$), 127.16 ($2C_{2'}$ or $2C_{3'}$), 128.19 ($C_4$), 128.26 ($2C_{2'}$ or $2C_{3'}$), 136.21 ($C_2$), 138.27 ($C_{1'}$), 165.72 (CONH), 169.77 ($COCH_3$) ppm; mass spectrum, FD (relative intensity) 274 ($M^+$+2, 12), 273 ($M^+$+1, 77), 272 (100), 205 (34), 274 (18).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 6.09; N, 20.32.

## EXAMPLE 77

Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole) acetamide.

A solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.60 g, 14.4 mmol) and $BBr_3$ (1M $CH_2Cl_2$ solution, 15.8 mL, 15.8 mmol)) was prepared in THF (250 mL) and cooled to −78° C. A solution of triethylamine (2.91 g, 28.8 mmol) in THF (20 mL) was then added to the above solution. This was followed by the addition of THF (30 mL) solution of pyrazole (1.17 g, 17.28 mmol) and the mixture thus obtained was stirred at −78° C. (30 min) and room temperature (1 h). The insoluble materials were filtered and the solvents removed from the filtrate in vacuo. The residue was then purified by flash column chromatography on silica gel using 4% MeOH/$CHCl_3$ as the eluant to give 0.80 g (22%) of the desired product. It was then recrystallized from EtOAc as a white solid: mp 158°–160° C.; $R_f$ 0.51 (6% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.93 (s, $COCH_3$), 4.29 (d, J=5.8 Hz, NH), 6.26 (s, $C_4H$), 6.57 (d, J=8.8 Hz, CH), 7.15–7.33 (m, 5PhH), 7.48 (br s, $C_5H$), 7.76 (br s, $C_3H$), 8.96 (t, J=5.8 Hz, NH), 9.23 (d, J=8.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.41 ($COCH_3$), 42.40 ($CH_2$), 65.51 (CH), 105.37 ($C_4$), 126.87 ($C_{4'}$), 127.14 ($2C_{2'}$ or $2C_{3'}$), 128.25 ($2C_{2'}$ or $2C_{3'}$), 129.00 ($C_5$), 138.59 ($C_3$), 139.17 ($C_{1'}$), 165.68 (CONH), 169.81 ($COCH_3$) ppm; mass spectrum, m/e (relative intensity) 273 ($M^+$+1, 11), 272 ($M^+$, 2), 139 (83), 138 (100), 92 (37).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 5.96; N, 20.28.

## EXAMPLE 78

Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole)) acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 17.6 mL, 17.6 mmol), $Et_3N$ (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g, 20.8 mmol), 1.20 g (28%) of the desired product was obtained. It was recrystallized from EtOAc as an amorphous white solid: mp 146°–148° C.; $R_f$ 0.48 (6% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, $COCH_3$), 4.32 (br s, $CH_2$), 6.70 (d, J=7.8 Hz, CH), 7.21–7.29 (m, 5PhH), 8.01 (s, $C_3H$), 8.57 (s, $C_5H$), 9.04 (br s, NH), 9.39 (d, J=7.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.39 ($COCH_3$), 42.59 ($CH_2$), 65.02 (CH), 126.97 ($C_{4'}$), 127.25 ($2C_{2'}$ or $2C_{3'}$), 128.32 ($2C_{2'}$ or $2C_{3'}$), 138.47 ($C_{1'}$), 143.93 ($C_5$), 151.50 ($C_3$), 164.77 (CONH), 170.23 ($COCH_3$) ppm; mass spectrum, FD (relative intensity) 275 ($M^+$+2, 12), 274 ($M^+$+1, 100), 273 (11), 205 (19), 204 (13), 140 (67), 139 (31).

Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37; H, 5.66; N, 25.38.

## EXAMPLE 79

Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole)) acetamide.

Making use of 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 13.2 mL, 13.2 mmol), $Et_3N$ (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6 mmol), 0.90 g (27%) of the desired product was obtained as a white solid. It was recrystallized from EtOH: mp 169°–171° C.; $R_f$ 0.22 (4% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.97 (s, $COCH_3$), 4.25–4.40 (m, $CH_2$), 7.05 (d, J=8.4 Hz, CH), 7.21–7.38 (m, 5PhH), 9.23 (t, J=5.5 Hz, NH), 9.44 (s, $C_5H$), 9.69 (d, J=8.4 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.38 ($COCH_3$), 42.78 ($CH_2$), 63.62 (CH), 127.10 ($C_{4'}$), 127.39 ($2C_{2'}$ or $2C_{3'}$), 128.38 ($2C_{2'}$ or $2C_{3'}$), 138.26 ($C_{1'}$), 143.67 ($C_5$), 163.88 (CONH), 170.62 ($COCH_3$), ppm; mass spectrum, FD (relative intensity) 275 ($M^+$ 79), 273 (14), 206 (100), 205 (50).

Anal. Calcd for $C_1H_{14}N_6O_2$: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75; H, 5.33; N, 30.64.

## EXAMPLE 80

Preparation of α-acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

Preparation of 2-acetamido-2-bromo-N-benzylacetamide.

A solution of 2-acetamido-2-ethoxy-N-benzylacetamide (2.00 g, 8 mmol) in dry $CH_2Cl_2$ (200 mL) was stirred at room temperature as a solution of $BBr_3$ (8.8 mL, 8.8 mmol, 1.0M in $CH_2Cl_2$) was introduced by means of a syringe under a nitrogen atmosphere. A while mist formed and alter it disappeared, the $N_2$ line was removed and the reaction

sealed. The resulting yellow solution was stirred (3.5 h) and then concentrated in vacuo to give yellow crystals of α-acetamido-2-bromo-N-benzyl acetamido which was stored under vacuum overnight.

Preparation of 2-pyridyllithium.

The generation of 2-pyridyllithium in situ was run under nitrogen. A solution of n-butyllithium (7.2 mL, 2.5M solution in hexane, 18 mmol) was added to dry ether (60 mL), cooled to −20° C., and stirred as 2-bromopyridine (1.6 mL, 17 mmol) in dry ether (15 mL,) was added dropwise (15 min). The resulting blood red solution was stirred at −20° C. for an additional 5 minutes and then transferred through a doubled-ended needle under a stream of nitrogen to an addition funnel where it was cooled to −78° C.

Preparation of α-acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The cooled 2-pyridyllithium solution was added dropwise (approximately 2 drops per second) to the solution of 2-acetamido-2-bromo-N-benzylacetamide in dry THF (200 mL) and maintained at −78° C. The reaction mixture was stirred for an additional 30–45 minutes at −78° C. The reaction was quenched with saturated aqueous solution of $NH_4Cl$ (40 mL) at −78° C. producing a heterogenous mixture $Na_2CO_3$ was added dropwise until the precipitate dissolved. The organic layer was separated and then the aqueous layer was extracted with ether (2×50 mL). The combined organic layers were dried ($Na_2SO_4$), concentrated under vacuum and separated using flash chromatography on silica gel with ethyl acetate as the eluent. The fractions containing the products were concentrated under vacuum, separated and then further purified by column chromatography on alumina (80–200 mesh, Grade 1, Fisher) employing ethyl acetate as the solvent. Fractions containing α-acetamido-N-benzyl-2-pyridylacetamide was concentrated to dryness and gave a white amorphous solid (250 mg, 11% yield); $R_f$=0.39 (5% $CH_3OH/CHCl_3$); mp 146°–147° C.; IR (KBr) 3290, 3180, 3020, 1620 br, 1580, 1520 br, 1480, 1420, 1370, 1310, 1260 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.96 (s, 3H), 4.28 (d, J=5.8 Hz, 2H), 5.59 (d, J=8.0 Hz, 1H), 7.18–7.30 (m, 5H), 7.32 (dd, J=7.7, 5.2 Hz, 1H), 7.47 (d, J=7.7 Hz, 1H), 7.80 (dt, J=7.7, 1.5 Hz, 1H), 8.55 (m, 2H), 8.78 (br t, J=5.8 Hz, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) 22.5, 42.1, 58.3, 121.7, 122.8, 126.6, 126.9 (2C), 128.1 (2C), 136.8, 139.1, 148.6, 157.2, 169.0, 169.2 ppm; FD (Lilly) mass spectrum, m/e (relative intensity) 284 ($M^+$+1, 6), 283 ($M^+$, 0.8), 151 (8), 150 (100), 141 (4). $C_{16}H_{17}N_3O_2$

Anal. Calcd for C 67.83, H, 6.05, N, 14.83

Found: C, 68.11, H, 6.00, N, 14.89.

Fractions containing 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide were combined, concentrated in vacuo and yielded a white amorphous solid: (150 mg, 6% yield). $R_f$ 0.34 (5% $CH_3OH/CHCl_3$); mp 226 decomposed (recrystallized in ethanol) $^1H$ NMR (300 MHx, DMSO-$d_6$) δ 1.94 s, 4.26 (dd, J=15.2, 5.7 Hz, 1H), 4.33 (dd, J=15.2, 6.1 Hz, 1H).6.26 (br t, J=6.8 Hz, 1H), 6.37 (br d, J=9.1 Hz, 1H), 6.69 (d, J=8.7 Hz, 1H), 7.22–7.33 (m, 5H), 7.42 (ddd, J=9.1, 6.8, 1.6 Hz, 1H), 7.58 (dd, J=6.8, 1.6 Hz, 1H), 8.93 (br t, J=5.8 Hz, 1H), 9.20 (d, J=8.7 Hz, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) 22.5, 42.5, 62.5, 105.1, 119.4, 126.80, 127.10 (2C), 128.2 (2C), 135.6, 138.8, 140.2, 161.2, 166.0, 170.0 ppm. Hydrogen and carbon assignments were verified with $^1H$-$^1H$ COSY, $^1H$-$^{13}C$-COSY, zero quantum NMR experiments. The structure was confirmed by X-ray crystallography.

Preparation of authentic 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The generation of 2-hydroxypyridylsodium in situ was done under anhydrous conditions. A solution of 2-hydroxypyridine (1.57 g, 16 mmol, vacuum dried, 97% Aldrich) in dry THF (200 mL) was stirred and cooled to 0° C. and then NaH (0.77 g, 60% in mineral oil, 19.2 mmol) was added in one portion leading to the evolution of $H_2$ and the generation of a heterogeneous mixture. A solution of 2-acetamido-2-bromo-N-benzylacetamide (8 mmol based on 2-acetamido-2-ethoxy-N-benzylacetamide) in dry THF (160 mL) was then transferred through a double-ended needle by means of a stream of nitrogen. The resulting mixture was quenched with saturated aqueous solution of $NH_4Cl$ (50 mL) at 0° C. producing a white precipitate. A saturated aqueous solution $Na_2CO_3$ was added dropwise while stirring at 0° C. until all of the white precipitate dissolved. The two layers were separated while cold and then the aqueous fraction was extracted with THF (2×100 mL). The combined organic layers were dried ($Na_2SO_4$), and concentrated to dryness. The crude reaction mixture residue was dissolved in a minimum of $CHCl_3$ and was flash chromatographed on a silica gel column using ethyl acetate as the eluent and gave a white amorphous solid (1.10 g, 46% yield) which was identical to properties previously observed for 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide: $R_f$ 0.34 (5% $CH_3OH/CHCl_3$); mp 162°–163.5° C. (recrystallized in ethyl acetate); IR (KBr) 3300, 3280, 3260, 3080, 1690, 1680, 1650 br, 1580, 1570, 1520, 1490, 1140 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.96 (s, 3H), 4.27 (dd, J=15.3, 5.8 Hz, 1H), 4.36 (dd, J=15.3, 6.2 Hz, 1H), 6.27 (dr, J=6.8, 1.1 Hz, 1H), 6.39 (bd, J=8.9 Hz, 1H), 6.71 (d, J=8.7 Hz, 1H), 7.22–7.34 (m, 5H), 7.43 (ddd, J=8.9, 6.8, 1.9 Hz, 1H), 7.59 (dd, J=6.8, 1.9 Hz, 1H), 8.93 (br t, J=5.9 Hz, 1H), 9.20 (d, J=8.7 Hz, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) 22.4, 42.5, 62.5, 105.1, 119.4, 126.8, 127.1 (2C), 128.2 (2C), 135.6, 138.8, 140.1, 161.1, 166.0, 169.9 ppm; FD (Lilly) mass spectrum m/e (relative intensity) 598 (2M, 2), 300 ($M^+$+1, 17), 299 ($M^+$, 100), 96 (2), 95 (26). $C_{16}H_{17}N_3O_3$.

Anal. Calcd for C, 64.20, H 5.73, N 14.04.

## EXAMPLE 81

α-acetamido-N-benzyl-2-pyridyl acetamide N-oxide

To a cooled solution of 2-α-acetamido-N-benzyl-2-pyridylacetamide dissolved in dry THF is added m-perchloroperbenzoic acid to give the resulting product.

Similarly, using the procedure described hereinabove, the following examples are prepared.

2-acetamido-N-benzyl-2-(3-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-pyrimidinyl)acetamide and the N-oxide thereof

2-acetamido-N-benzyl-2-(4-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(5-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(3-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyrazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-thiazolyl)acetamide,

2-acetamido-N-benzyl-2-(2-oxazolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isoxazolyl)acetamide,

2-acetamido-N-benzyl-2-(5-isoxatolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isothiazolyl)acetamide, and 2-acetamido-N-benzyl-2-(5-isothiazolyl)acetamide.

General Procedure.

2-Acetamido-N-benzyl-2-ethoxyacetamide (1 equiv.) was suspended in anhydrous ethyl ether, and then boron trifluoride etherate (1.6–6.3 equiv.) was rapidly added and the resulting solution was stirred for 15 min. The aromatic substrate (1.6–16 equiv.) was then added and the reaction was stirred at room temperature (1–7 days).

## EXAMPLE 82

α-Acetamido-N-benzyl-2-(S-thiophenoxy)-acetamide (II).

The reaction mixture was treated with an aqueous saturated $NaHCO_3$ solution and the white insoluble solid was filtered and then washed successively with $H_2O$ and hexanes. The desired product was purified by recrystallization from chloroform hexanes to give II in 94% yield: $R_f$ 0.43 (97:3 chloroform/methanol): m.p. 165°–167°: i.r. (KBr) 3280, 1630 (br), 1520 (br), 1430, 1365, 1280, 1245, 1180 $cm^{-1}$; $^1H$ n.m.r. (DMSO-$d_6$) 81.83 (s, $CH_3CO$). 4.22–4.36 (m, $CH_2$). 5.90 (d, J=9.0 Hz, NH), 8,84 (t, J=5.4 Hz, NH); $^{13}C$ n.m.r. (DMSO-$d_6$) 22.34 ($CH_3CO$), 42.25 ($CH_2$), 57.65 (CH). 126.86 ($C_4$'), 127.20 ($2C_2$') 123.73 ($C_4$'). 128.28 ($2C_2$' or $2C_3$'), 128.88 ($2C_2$' or $2C_3$'), 132.36 ($2C_3$'), 132.51 ($C_1$'), 138.76 ($C_1$'). 167.09 (CONH) 168.97 ($CH_3CO$)ppm; mass spectrum, m/e (relative intensity) 315 (M+1,1), 205 (17), 163 (40), 138 (8), 110 (90), 109 (29), 106 (96), 93 (35), 91 (100).

Anal. calc. for $C_{17}H_{18}N_2O_2S$: C 64.94, H 5.77. Found: C 65.27, H 5.54.

## EXAMPLE 83

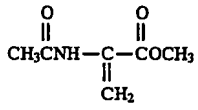
Synthesis of α-Acetamido-N-benzyl-2-(tetrahydrofuran) acetamide (3).

A methanolic solution (70 mL) of α-acetamido-N-benzyl-2-furanacetamide (3.50 g, 12.85 mmol) was hydrogenated (35–40 psi) in the presence of Pd/C (10%, 0.44 g) (44 h). The catalyst was filtered through celite, washed with MeOH (10 mL) and the filtrate concentrated to dryness in vacuo to give 3a and 3b (3.50 g) as a white solid. The products were fractionally recrystallized from EtOAc to give 1.30 g (37%) of 3a: mp 159°–161° C.; $R_f$ 0.38 (6% MeOH/$CHCl_3$); IR (KBr) 3340 (br), 3000, 1600, 1550 (br), 1420, 1350, 720, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.66–1.90 (m, $C_3H_2$, $C_4H_2$), 1.85 ($C(O)CH_3$), 3.62–3.68 (m, $C_5HH'$), 3.75–3.80 (m, $C_5HH'$), 3.98–4.00 (m, $C_2H$), 4.26–4.38 (m, CH, $CH_2$), 7.18–7.32 (m, 5 PhH), 8.11 (d, J=8.8 Hz, NH), 8.52 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.52 ($C(O)CH_3$), 24.78 ($C_3$), 27.82 ($C_4$), 41.96 ($CH_2$), 55.67 (CH), 67.54 ($C_5$), 78.48 ($C_2$), 126.58 ($C_4$'), 127.97 ($2C_2$' or $2C_3$'), 128.12 ($2C_2$' or $2C_3$'). 139.27 ($C_1$'), 169.09 (C(O)NH), 170.09 ($C(O)CH_3$) ppm; mass spectrum m/e (relative intensity) 277 ($M^+$+1, 4), 206 (52), 142 (13), 106 (38), 91 (100), 71 (97). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

The remaining EtOAc mother liquor after recrystallization was concentrated to half its volume and hexane was added dropwise while heating until the solution became turbid. A white solid (0.65 g, 18%) separated on cooling and was collected by filtration to give diastereoisomer 3b: mp 130°–132° C.; $R_f$ 0.38 (6% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.55–1.86 (m, $C_3H_2$, $C_4H_2$), 1.89 $C(O)CH_3$), 3.55–3.64 (m, $C_5HH'$), 3.70–3.78 (m, $C_5HH'$), (s, 4.08–4.11 (m, $C_2H$), 4.27 (d, J=5.8 Hz, $CH_2$), 4.36 (dd, J=4.7, 8.6 Hz, CH), 7.21–7.32 (m, 5 PhH), 7.94 (d, J=8.6 Hz, NH), 8.39 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.45 ($C(O)CH_3$), 25.16 ($C_4$), 27.53 ($C_3$), 42.04 ($CH_2$), 55.48 (CH), 67.53 ($C_5$), 78.26 ($C_2$), 126.59 ($C_4$'), 127.04 ($2C_2$' or $2C_3$'), 128.10 ($2C_2$' or $2C_3$'), 139.21 ($C_1$'), 169.55 (C(O)NH), 169.79 ($C(O)CH_3$) ppm; mass spectrum m/e (relative intensity) 277 ($M^+$+1, 4), 206 (50), 142 (23), 106 (39), 1 (100), 71 (96). Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

## EXAMPLE 84

Synthesis of Methyl α-Acetamido-2-methyl-2-furanacetate (17). HBr was bubbled (2.5 min) through a $CDCl_3$ solution (25 mL) of 15 (3.80 g, 26.6 mmol). The excess HBr and $CDCl_3$ were removed by evaporating the solution with a continuous stream of Ar (20–30 min). The light yellow oily residue that remained containing 16 was dissolved in THF (100 mL), and then furan (32.76 g, 482.0 mmol) and $ZnCl_2$ (1M in ether, 53.0 mL, 53.0 mmol) were added. The reaction was stirred at room temperature (3.5 h) and then treated with $H_2O$ (50 mL). The aqueous mixture was extracted with EtOAc (3×100 mL), and the combined extracts were dried ($Na_2SO_4$). The volatile materials were removed by distillation in vacuo to give 5.00 g (89%) of 17: $R_f$ 0.35 (50%, EtOAc/$CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.94 (s, $CH_3$), 1.99 (s, $C(O)CH_3$), 3.74 (s, $C(O)OCH_3$), 6.36 (br s, $C_3H$, $C_4H$), 6.83 (s, NH), 7.35 (s, $C_5H$); $^{13}C$ NMR ($CDCl_3$) 21.43 ($CH_3$), 23.26 ($C(O)CH_3$), 53.03 ($C(O)OCH_3$), 58.36 ($C(OH_3)$), 107.39 ($C_4$), 110.52 ($C_3$), 142.10 ($C_5$), 152.03 ($C_2$), 169.21 ($C(O)CH_3$), 171.34 ($C(O)OCH_3$) ppm.



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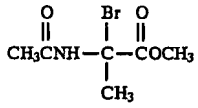

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## EXAMPLE 85

Synthesis of α-Acetamido-2-methyl-2-furanacetic Acid (18).

A 95% EtOH solution (150 mL) of 17 (5.00 g, 23.6 mmol) and KOH (3.00 g, 53.5 mmol) was stirred at room temperature (48 h). The solvent was removed and the residue was dissolved in $H_2O$ (50 mL). The aqueous solution was washed with $Et_2O$ (3×50 mL) and then acidified to pH 1.5 with 10% $H_3PO_4$. The acidified solution was extracted with EtOAc (3×200 mL) and the combined extracts were dried ($Na_2SO_4$), and concentrated in vacuo to give 2.90 g (62%) of 18: mp 178°–180° C. (d) (recrystallized from $CH_3CN$); IR (KBr) 3400 (br), 1700 (br) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.67 (s, $CH_3$), 1.83 (s, $C(O)CH_3$), 6.39 (m, $C_3H$, $C_4H$), 7.59 (s, $C_5H$), 8.34 (s, NH), 12.63 (s, C(O)OH); $^{13}C$ NMR (DMSO-$d_6$) 22.20 ($C(O)CH_3$), 22.59 ($CH_3$), 57.65 ($C(CH_3)$), 107.09 ($C_4$), 110.49 ($C_3$), 142.33 ($C_5$), 153.36 ($C_2$), 168.86 (C(O)NH), 171.78 (C(O)OH) ppm; mass spectrum, m/e (relative intensity) 198 ($M^+$+1, 4), 143 (97), 152 (63), 140 (23), 111 (73), 110 (100), 94 (24). Anal. ($C_9H_{11}NO_4$) C, H, N.

## EXAMPLE 86

Synthesis of α-Acetamido-N-benzyl-2-methyl-2-furanacetamide (4).

Employing the mixed carbonic anhydride coupling procedure with 18 (2.40 g, 12.2 mmol), 4-methylmorpholine (1.23 g, 12.2 mmol), isobutylchloroformate (1.83 g, 13.4 mmol), and benzylamine (1.43 g, 12.7 mmol) gave 4 (1.50

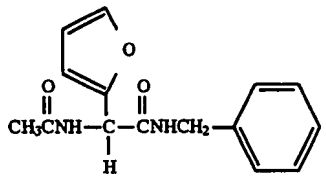
g, 43%) as a thick oil: $R_f$ 0.29 (2% MeOH/$CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.94 (s, $CH_3$), 1.98 (s, $C(O)CH_3$), 4.40 (d, J=5.6 Hz, $CH_2$), 6.20 (br s, NH), 6.34–6.37 (m, $C_3H$, $C_4H$), 7.05–7.36 (m, NH, $C_5H$, 5 PhH); $^{13}C$ NMR ($CDCl_3$) 22.31 ($C(O)CH_3$), 23.81 ($CH_3$), 43.77 ($CH_2$), 58.50 ($C(CH_3)$), 107.94 ($C_4$), 110.67 ($C_3$), 126.99 ($2C_2'$ or $2C_3'$), 127.41 ($C_4'$), 128.60 ($2C_2'$ or $2C_3'$), 137.52 ($C_1'$), 142.38 ($C_5$), 152.94 ($C_2$), 169.03 (C(O)NH), 171.16 ($COCH_3$) ppm; mass spectrum, m/e (relative intensity) 287 ($M^+$+1, 4), 228 (4), 153 (99), 152 (96), 138 (15), 111 (63), 110 (100), 91 (75); $M_r$ (EI) 286.13074 (calcd for $C_{16}H_{18}N_2O_3$, 286.13174).

## EXAMPLE 87

Synthesis of α-Thioacetamido-N-benzyl-2-furanacetamide (5).

A THF solution (80 mL) of 2 (1.00 g, 3.68 mmol) and Lawesson's reagent (0.73 g, 1.84 mmol) was stirred at room temperature (4 h). The THF was removed in vacuo and the residue was purified by flash column chromatography on $SiO_2$ gel using 1% MeOH/$CHCl_3$ to give 0.75 g (71%) of 5: mp 78°–80° C.; $R_f$ 0.51 (1% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 1630, 1500, 1440, 1350, 790, 710, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.46 (s, $C(S)CH_3$), 4.27–4.35 (m, $CH_2$), 6.22 (d, J=7.7 Hz, CH), 6.32 (d, J=3.3 Hz, $C_3H$), 6.41–6.44 (m, $C_4H$), 7.15–7.33 (m, 5 PhH), 7.64 (s, $C_5H$), 8.81 (t, J=5.9 Hz, NH), 10.54 (d, J=7.7 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 32.70 (s, $C(S)CH_3$), 42.39 ($C_2$), H 56.82 (CH), 108.76 ($C_3$), 110.67 ($C_4$), 126.81 ($C_4'$), 127.12 ($2C_2'$ or $2C_3'$), 128.23 ($2C_2'$ or $2C_3'$), 139.98 ($C_1'$), 143.06 ($C_5$), 149.53 ($C_2$), 166.55 (C(O)NH), 200.68 ($C(S)CH_3$) ppm; mass spectrum (FD) 288 ($M^+$). Anal. ($C_{15}H_{16}N_2O_2S$) C, H, N.

2

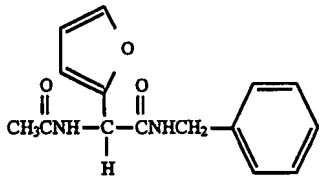


## EXAMPLE 88

Synthesis of α-Thioacetamido-N-benzyl-2-furanthioacetamide (6).

A THF solution (90 mL) of 2 (2.00 g, 7.35 mmol) and Lawesson's reagent (3.27 g, 8.09 mmol) was heated to reflux (4 h). The THF was removed in vacuo and the residue was purified by two successive flash column chromatographies on $SiO_2$ gel using 0.5% MeOH/$CHCl_3$ as the eluant in the first chromatography and $CHCl_3$ in the second chromatography. Compound 6 (0.50 g, 22%) was then further purified by preparative TLC ($CHCl_3$): mp 99°–101° C.; $R_f$ 0.74 (1% MeOH/$CHCl_3$); IR (KBr) 3100, 1580, 1500 (br) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 2.58 (s, $C(S)CH_3$), 4.86 (dd, J=5.4, 15.0 Hz, CHH), 4.96 (dd, J=5.4, 15.0 Hz, CHH), 6.49–6.55 (m, $C_3H$, $C_4H$), 6.65 (d, J=7.5 Hz, CH), 7.31–7.43 (m, 5 PhH), 7.75 (s, $C_5H$) 10.64 (d, J=7.5 Hz, NH), 10.95 (t, J=5.4 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 32.79 (s, $C(S)CH_3$), 48.30 ($CH_2$), 61.88 (CH), 108.50 ($C_3$), 110.53 ($C_4$), 127.05 ($C_4'$), 127.48 ($2C_2'$ or $2C_3'$), 128.19 ($2C_2'$ or $2C_3'$), 136.67 ($C_1'$), 142.91 ($C_5$), 150.15 ($C_2$), 197.45 (C(S)NH), 200.56 ($C(S)CH_3$) ppm; mass spectrum (FD) 304 ($M^+$). Anal. ($C_{15}H_{16}N_2OS_2$) C, H, N.

2



## EXAMPLE 89

Synthesis of α-Acetamido-N-(3-pyridinylmethyl)-2-furanacetamide (7).

Using racemic 19 (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39 mmol), isobutylchloroformate (2.24 g, 16.39 mmol), and 3-aminomethylpyridine (1.77 g, 16.39 mmol) in the mixed carbonic anhydride protocol gave 3.35 g (75%) of 7: mp 172°–174° C. (recrystallized from EtOAc); $R_f$ 0.27 (8% MeOH/$CHCl_3$); IR (KBr) 3400, 3300, 1640, 1540, 1420, 1360, 820, 740 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.32 (d, J=5.8 Hz, $CH_2$), 5.55 (d, J=7.9 Hz, CH), 6.28–6.29 (m, $C_3H$), 6.41–6.43 (m, $C_4H$), 7.32 (dd, J=4.8, 7.7 Hz, $C_5'H$), 7.58–7.62 (m, $C_4'H$, $C_5H$), 8.44 (br s, $C_2'H$, $C_6'H$), 8.62 (d, J=7.9 Hz, NH), 8.81 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.31 ($C(O)CH_3$), 39.98 ($CH_2$), 50.94 (CH), 107.67 ($C_4$), 110.54 ($C_3$), 123.38 ($C_5'$), 134.57 ($C_3'$), 134.83 ($C_4'$), 142.64 ($C_5$), 148.06 ($C_6'$), 148.55 ($C_2'$), 150.94 ($C_2$), 168.19 (C(O)NH), 169.26 ($C(O)CH_3$) ppm; mass spectrum (FD) 274 ($M^+$+1). Anal. ($C_{14}H_{15}N_3O_3$) C, H, N.

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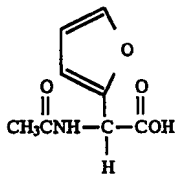
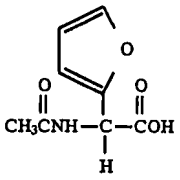


## EXAMPLE 90

Synthesis of α-Acetamido-N-(4-pyridinylmethyl)-2-furanacetamide (8).

Making use of racemic 19 (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39 mmol), isobutylchloroformate (2.24 g, 16.39 mmol), and 4-aminomethylpyridine (1.77 g, 16.39 mmol) in the mixed carbonic anhydride method, gave 3.40 g (76%) of 8: mp 168°–170° C. (recrystallized from EtOAc); $R_f$ 0.31 (8% MeOH/$CHCl_3$); IR (KBr) 3180, 1650 (br), 1480, 1400, 1340, 780, 740 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.90 (s, $C(O)CH_3$), 4.32 (d, J=5.7 Hz, $CH_2$), 5.57 (d, J=7.8 Hz, CH), 6.32–6.34 (m, $C_3H$), 6.42–6.43 (m, $C_4H$), 7.19 (d, J=4.9 Hz, $C_3'H$, $C_5'H$), 7.64 (s, $C_5H$), 8.46 (d, J=4.9 Hz, $C_2'H$, $C_6'H$), 8.64 (d, J=7.8 Hz, NH), 8.84 (t, J=5.7 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.27 ($C(O)CH_3$), 41.26 ($CH_2$), 50.99 (CH), 107.74 ($C_4$), 110.54 ($C_3$), 121.87 ($C_3'$, $C_5'$), 142.63 ($C_5$), 148.17 ($C_4'$), 149.35 ($C_2'$, $C_6'$), 150.82 ($C_2$), 168.35 (C(O)NH), 169.29 (C(O)$CH_3$) ppm; mass spectrum (FD) 274 ($M^+$+1). Anal. ($C_{14}H_{15}N_3O_3$) C, H, N.



EXAMPLE 91

Synthesis of α-Acetamido-N-(1-oxo-3-pyridinylmethyl)-2-furanacetamide (9).

A solution of 7 (1.50 g, 5.49 mmol) and m-chloroperoxybenzoic acid (1.90 g, 6.04 mmol) in THF (175 mL) was heated to reflux (3 h) and then cooled to room temperature. The THF solution was concentrated to approximately half its volume, and then cooled to give 1.00 g (63%) of 9: mp 159°–161° C. (recrystallized from EtOH); $R_f$ 0.30 (20% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 1620, 1500 (br), 1420, 1350, 750 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.27 (d, J=5.0 Hz, $CH_2$) 5.53 (d, J=7.6 Hz, CH), 6.31 (br s, $C_3H$), 6.42 (br s, $C_4H$), 7.14–7.18 (m, 1 ArH), 7.34–7.37 (m, 1 ArH), 7.61 (br s, $C_5H$), 8.07 (s, 2 ArH), 8.63 (br s, NH), 8.80 (br s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.29 ($C(O)CH_3$), 39.36 ($CH_2$), 50.99 (CH), 107.79 ($C_4$), 110.56 ($C_3$), 124.03 ($C_4'$), 126.10 ($C_5'$), 137.16 ($C_3'$), 137.31 ($C_6'$), 138.70 ($C_2'$), 142.69 ($C_5$), 150.72 ($C_2$), 168.40 (C(O)NH), 169.32 ($C(O)CH_3$) ppm; mass spectrum (FD) 289 ($M^+$); $M_r$ (EI) 289.10554 (calcd for $C_{14}H_{15}N_3O_4$, 289.10626).

Anal. Calcd for $C_{14}H_{15}N_3O_4.2.0\ H_2O$: C, 51.69; H, 5.89; N, 12.92. Found: C, 52.03; H, 5.56; N, 13.36.

EXAMPLE 92

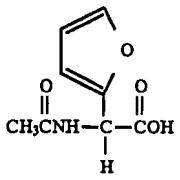
Synthesis of α-Acetamido-N-(1-oxo-4-pyridinylmethyl)-2-furanacetamide (10).

Following the preceding procedure and using 8 (1.50 g, 5.49 mmol) and m-chloroperoxybenzoic add (1.90 g, 6.04 mmol) gave a light yellow solid (0.96 g, 60%) directly upon cooling the THF solution. The precipitate was filtered and recrystallized from EtOH to give 10: mp 210°–212° C. (d); $R_f$ 0.25 (20% MeOH/$CHCl_3$); IR (KBr) 3300, 1620, 1500, 1410, 1350, 740 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.26 (d, J=5.8 Hz, $CH_2$), 5.52 (d, J=7.7 Hz, CH), 6.30 (br s, $C_3H$), 6.41–6.42 (m, $C_4H$), 7.21 (d, J=6.8 Hz, $C_3'H$, $C_5'H$), 7.63 (s, $C_5H$), 8.14 (d, J=6.8 Hz, $C_2'H$, $C_6'H$), 8.62 (d, J=7.7 Hz, NH), 8.82 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.35 ($C(O)CH_3$), 40.68 ($CH_2$), 51.14 (CH), 107.87 ($C_4$), 110.62 ($C_3$), 124.83 ($C_3'$, $C_5'$), 137.43 ($C_4'$), 138.39 ($C_2'$, $C_6'$), 142.72 ($C_5$), 150.77 ($C_2$), 168.48 (C(O)NH), 169.45 ($C(O)CH_3$) ppm; mass spectrum (FD) 289 ($M^+$). Anal. ($C_{14}H_{15}N_3O_4$) C, H, N.

EXAMPLE 93

Synthesis of α-Acetamido-2-furanacetic-2'-pyridinehydrazide (11).

Following the mixed carbonic anhydride procedure and using racemic 19 (2.00 g, 10.39 mmol), 4-methylmorpholine (1.10 g, 10.93 mmol), isobutylchloroformate (1.49 g, 10.93 mmol), and 2-hydrazinopyridine (1.20 g, 11.00 mmol) gave an insoluble material upon workup containing 11 and 4-methylmorpholine hydrochloride. The reaction products were suspended in EtOH (25 mL), and 11 (1.00 g) was collected by filtration. Concentration of the THF filtrate and trituration of the residue with EtOAc gave an additional 0.70 g of 11 to give a combined yield of 1.70 g (64%): mp 226°–228° C. (recrystallized from EtOH); $R_f$ 0.30 (10% MeOH/$CHCl_3$); IR (KBr) 3400, 1650, 1580, 1440, 1360, 1320, 770, 730 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, $C(O)CH_3$), 5.64 (d, J=8.0 Hz, CH), 6.41–6.50 (m, $C_3H$, $C_4H$, $C_5'H$), 6.67 (dd, J=5.4, 6.7 Hz, $C_3'H$), 7.44–7.52 (m, $C_4'H$), 7.66 (s, $C_5H$), 8.02 (d, J=4.0 Hz, $C_6'H$), 8.40 (s, C(O)NHNH), 8.66 (d, J=8.0 Hz, NH), 10.20 (s, C(O)NHNH); $^{13}C$ NMR (DMSO-$d_6$) 22.26 ($C(O)CH_3$), 49.56 (CH), 105.93 ($C_3'$), 107.87 ($C_3$), 110.57 ($C_4$), 114.50 ($C_5'$), 137.48 ($C_4'$), 142.76 ($C_5$), 147.45 ($C_6'$), 150.60 ($C_2$), 159.59 ($C_2'$), 167.88 (C(O)NH), 169.28 ($C(O)CH_3$) ppm; mass spectrum (FD) 274 ($M^+$); $M_r$ (EI) 274.10649 (calcd for $C_{13}H_{14}N_4O_3$, 274.10659).



EXAMPLE 94

Synthesis of R(−) α-Acetamido-N-(4-fluorobenzyl)-2-furanacetamide ((R)-12).

Using (R)-19 (0.94 g, 5.1 mmol), 4-methylmorpholine (0.52 g, 5.1 mmol), isobutylchloroformate (0.70 g, 5.1 mmol), and 4-fluorobenzylamine (0.65 g, 5.16 mmol) in the mixed carbonic anhydride method gave 1.00 g (68%) of (R)-12: mp 205°–207° C. (recrystallized from EtOAc); $R_f$ 0.30 (4% MeOH/$CHCl_3$); $[\alpha]^{26}_D$=−77.42 (c=1, MeOH); IR (KBr) 3400 (br), 1620, 1580, 1500 (br), 1350, 770, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.27 (d, J=5.9 Hz, $CH_2$), 5.54 (d, J=8.0 Hz, CH), 6.27 (d, J=3.0 Hz, $C_3H$), 6.41 (dd, J=1.9, 3.0 Hz, $C_4H$), 7.08–7.15 (m, 2 ArH), 7.20–7.26 (m, 2 ArH), 7.61 (d, J=1.9 Hz, $C_5H$), 8.58 (d, J=8.0 Hz, NH), 8.74 (t, J=5.9 Hz, NH) ppm; addition of R(−) mandelic add to a $CDCl_3$ solution of (R)-12 gave only one signal for the acetamide methyl protons. Mass spectrum (FD) 290 ($M^+$) Anal. ($C_{15}H_{15}FN_2O_3$) C, H, N.

Synthesis of R(−)α-Acetamido-N-(4-methylbenzyl)-2-furanacetamide ((R-13).

Employing the mixed carbonic anhydride procedure and making use of (R)-19 (1.50 g, 8.20 mmol), 4-methylmorpholine (0.83 g, 8.20 mmol), isobutylchloroformate (1.12 g, 8.20 mmol), and 4-methylbenzylamine (0.99 g, 8.20 mmol) gave 1.80 g (77%) of (R)-13: mp 210°–212° C. (recrystallized from EtOAc); $R_f$ 0.54 (4% MeOH/$CHCl_3$); $[\alpha]^{26}_D$=−74.43 (c=1, MeOH); IR (KBr) 3400 (br), 1610 (br), 1500 (br), 1350, 1320, 780, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 2.25 (s, $CH_3$), 4.24 (d, J=5.5 Hz, $CH_2$), 5.56 (d, J=8.1 Hz, CH), 6.28 (br s, $C_3H$), 6.41 (br s, $C_4H$), 7.09 (br s, 4ArH), 7.61 (br s, $C_5H$), 8.58 (d, J=8.1 Hz, NH), 8.72 (t, J=5.5 Hz, NH) addition of (R)-(−)mandelic acid to a $CDCl_3$ solution of (R)-13 gave only one signal for the acetamide methyl protons. $^{13}C$ NMR (DMSO-$d_6$) 20.64 ($CH_3$), 22.32 ($C(O)CH_3$), 42.00 ($CH_2$), 50.88 (CH), 107.52 ($C_4$), 110.50 ($C_3$), 127.06 ($2C_2'$ or $2C_3'$), 128.77 ($2C_2'$ or $2C_3'$), 135.82 ($C_1'$ or $C_4'$), 135.98 ($C_1'$ or $C_4'$), 142.51 ($C_5$), 151.21 ($C_2$) 167.87 (C(O)NH), 169.17 ($C(O)CH_3$) ppm; mass spectrum (FD) 287 ($M^+$+1). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

EXAMPLE 95

Synthesis of R(−)α-Acetamido-N-(4-trifluoromethylbenzyl)-2-furanacetamide ((R)-14).

Using (R)-19 (1.00 g, 5.46 mmol), 4-methylmorpholine (0.55 g, 5.46 mmol), isobutylchloroformate (0.75 g, 5.46 mmol), and 4-trifluoromethylbenzylamine (0.96 g, 5.46 mmol) in the mixed carbonic anhydride protocol gave 1.15 g (59%) of (R)-14: m.p 193°–195° C. (recrystallized from EtOAc/hexane); $[\alpha]^{26}_D$=–69.27 (c=1, MeOH); IR (KBr) 3220, 1610, 1520, 1400, 1350, 800, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.37 (d, J=5.8 Hz, $CH_2$), 5.56 (d, J=7.9 Hz, CH), 6.30–6.31 (m, $C_3H$), 6.41–6.43 (m, $C_4H$), 7.40–7.43 (m, 2ArH), 7.63–7.68 (m, 2ArH, $C_5H$), 8.62 (d, J=7.9 Hz, NH), 8.44 (t, J=5.8 Hz, NH); addition of (R)(–)-mandelic acid to a $CDCl_3$ solution of (R)-14 gave only one signal for the acetamide methyl protons. Mass spectrum (FD) 340 ($M^+$). Anal. ($C_{16}H_{15}F_3N_2O_3$) C, H, N.

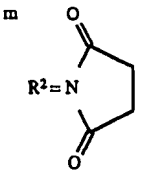
## GENERAL SYNTHESIS

General Synthesis—Several preparative routes were utilized for the construction of the targetted compounds. In most cases, 2-acetamido-N-benzyl-2-aminoacetamide (2r) served as the starting material. Treatment of 2r with the appropriate chloroformate, isocyanate, isothiocyanate, arthydride, or use of the mixed anhydride protocol advanced for peptide synthesis led to the preparation of the N-acyl substituted adducts 2e–2l and 2n. Correspondingly, the preformed α-bromo derivative 2s was employed as the immediate precursor for 2m and 2p, while 2-acetamido-N-benzyl-2-(trimethylammonio)acetamide tetrafluoroborate (2t) was utilized for the synthesis of 2o. Finally, alkaline hydrolysis of 2p, followed by neutralization of the dipeptide by passage through an ion exchange resin yielded 2g.

In Examples 96–108, reference is made to the following compounds

2a $R^2$ = $NHCH_2CH_3$
b $R^2$ = $NHNHCO_2CH_2Ph$
c $R^2$ = $NH(OCH_3)$
d $R^2$ = $N(CH_3)OCH_3$
e $R^2$ = $NHC(O)OCH_3$
f $R^2$ = $NHC(O)OPh$
g $R^2$ = $NHC(O)NHCH_3$
h $R^2$ = $NHC(O)NHPh$
i $R^2$ = $NHC(O)NHS(O_2)Ph$
j $R^2$ = $NHC(S)NHCH_3$
k $R^2$ = $NHC(S)NHPh$
l $R^2$ = $NHC(O)Ph(2'CO_2H)$

m



n $R^2$ = $NHC(O)CH_2NHC(O)OCH_2Ph$
o $R^2$ = $NHCH_2C(O)OCH_2CH_3$
p $R^2$ = $NHCH_2C(O)OCH_2Ph$
q $R^2$ = $\overset{+}{N}H_2CH_2CO_2^-$
r $R^2$ = $NH_2$
s $R^2$ = Br
t $R^2$ = $\overset{+}{N}(CH_3)_3, BF_4^-$
u $R^2$ = $NHC(O)CH_3$
v $R^2$ = $NHC(O)CF_3$

## EXAMPLE 96

Chemistry—Synthesis of Methyl[acetamido (benzylcarbamoyl)methyl]carbomate (2e).

Methyl chloroformate (0.33 g, 3.35 mmol) was added to a solution 2r (0.70 g, 3.16 mmol) and $Et_3N$ (0.39 g, 3.80 mmol) in THF (75 mL), and then the reaction mixture was stirred at 55°–60° C. (2 h). The $Et_3N.HCl$ that precipitated was filtered and the filtrate was concentrated to dryness in vacuo. The residue was triturated with EtOAc (20 mL), and the remaining white solid (0.55 g, 62%) was filtered and recrystallized from EtOH: mp. 202°–204° C. (d); $R_f$ 0.53 (10% MeOH/$CHCl_3$); IR (KBr) 3260, 1650, 1500, 1440, 1360, 780, 690 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.86 (s, $C(O)CH_3$), 3.54 (s, $OCH_3$), 4.27 (d, J=5.6 Hz, $CH_2$), 5.56 (t, J=7.8 Hz, CH), 7.18–7.32 (m, 5PhH), 7.70 (br s, NHC(O)$OCH_3$), 8.40 (d, J=7.8 Hz, NH), 8.51 (t, J=5.6 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.38 ($C(O)CH_3$), 42.29 ($CH_2$), 51.46 ($OCH_3$), 58.57 (CH), 126.52 ($C_4$'), 126.98 ($2C_2$' or $2C_3$'), 127.99 ($2C_2$' or $2C_3$'), 139.03 ($C_1$'), 167.83 (C(O)NH), 169.33 ($C(O)CH_3$) ppm, the carbamate carbonyl signal was not detected. Mass spectrum (FD) 279 ($M^+$).

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 56.16; H, 6.10; N, 14.89.

## EXAMPLE 97

Synthesis of Phenyl[acetamido(benzylcarbamoyl)methyl] carbamate (2f).

Compound 2r (0.80 g, 3.62 mmol) was dissolved in warm THF (75 mL), and then $Et_3N$ (0.44 g, 4.35 mmol), and phenyl chloroformate (0.62 g, 3.98 mmol) were added. The reaction mixture was stirred at 45°–50° C. (2 h), and the volatile materials were removed in vacuo. The residue was triturated with EtOAc (20 mL) and the remaining white solid material (0.80 g, 65%) was filtered, washed with $H_2O$ (10 mL), and then recrystallized from MeOH: mp 201°–203° C.; $R_f$ 0.38 (5% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 3240, 1700, 1630, 1500, 1460, 1320, 1200, 740, 600 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, $C(O)CH_3$), 4.29–4.35 (m, $CH_2$), 5.66 (t, J=7.6 Hz, CH), 7.08–7.42 (m, 10ArH), 8.43 (d, J=7.6 Hz, NH), 8.58 (d, J=7.6 Hz, NH), 8.67 (t, J=5.0 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.58 ($C(O)CH_3$), 42.51 ($CH_2$), 58.69 (CH), 121.70 ($2C_2$), 125.18 ($C_4$), 126.76 ($C_4$'), 127.19 ($2C_2$' or $2C_3$'), 128.21 ($2C_2$' or $2C_3$'), 129.30 ($2C_3$), 139.14 ($C_1$'), 150.91 ($C_1$), 167.73 (C(O)NH), 169.75 ($C(O)CH_3$) ppm, the signal for the carbamate carbonyl was not detected. Mass spectrum (FD) 341 ($M^+$).

Anal. Calcd for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.06; H, 5.64; N, 12.12.

## EXAMPLE 98

Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylurea (2g).

Methyl isocyanate (0.20 g, 3.48 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 45°–50° C. (2 h). The white solid (0.80 g, 91%) that separated out was filtered and recrystallized from MeOH to give 2g: mp 229°–230° C. (d); $R_f$ 0.25 (10% MeOH/$CHCl_3$); IR (KBr) 3200, 3060, 1630, 1500 (br), 1350, 1300, 740, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.82 (s, $C(O)CH_3$), 2.54 (d, J=4.5 Hz, $NHCH_3$), 4.26 (d, J=5.8 Hz, $CH_2$), 5.59 (t, J=7.8 Hz, CH), 6.19 (d, J=4.5 Hz, $NHCH_3$), 6.52 (d, J=7.8 Hz, NHC(O)$NHCH_3$), 7.20–7.31 (m, 5PhH), 8.38 (t, J=5.8 Hz, NH), 8.46 (d, J=7.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.36 ($C(O)CH_3$), 26.03 ($NHCH_3$), 42.19 ($CH_2$), 57.92 (CH), 126.54 ($C_4$'), 126.93 ($2C_2$' or $2C_3$'), 128.06 ($2C_2$' or $2C_3$'), 139.16 ($C_1$'), 157.30 (NHC(O)NH), 168.89 (C(O)NH), 169.37 ($C(O)CH_3$) ppm; mass spectrum (FD) 279 ($M^+$+1).

Anal. Calcd for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13. Found: C, 56.31; H, 6.41; N, 20.12.

EXAMPLE 99

Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylurea (2h).

Phenyl isocyanate (0.42 g, 3.5 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 45°–50° C. (2 h). The white solid (0.95 g, 89%) that precipitated was filtered and dried: mp 242°≧244° C. (d); $R_f$ 0.30 (5% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 1600 (br), 1430 (br), 1300, 880, 700 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.86 (s, C(O)$CH_3$), 4.30 (d, J=5.9 Hz, $CH_2$), 5.67 (t, J=7.6 Hz, CH), 6.86–6.93 (m, 2ArH), 7.20–7.32 (m, NH, 5PhH, 1ArH), 7.37–7.40 (m, 2ArH), 8.56 (t, J=5.9 Hz, NH), 8.68 (d, J=7.6 Hz, NH), 8.89 (s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.38 (C(O)$CH_3$), 42.29 ($CH_2$), 57.59 (CH), 117.61 ($2C_2$), 121.37 ($C_4$), 126.57 ($C_{4'}$), 126.95 ($2C_{2'}$ or $2C_{3'}$), 128.07 ($2C_{2'}$ or $2C_{3'}$), 128.62 ($2C_3$), 139.12 ($C_1$ or $C_{1'}$), 139.98 ($C_1$ or $C_{1'}$), 153.98 (NHC(O)NH), 168.55 (C(O)NH), 169.58 (C(O)$CH_3$) ppm; mass spectrum (FD) 340 ($M^+$).

Anal. Calcd for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.72; H, 5.92; N, 16.20.

EXAMPLE 100

Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-benzenesulfonylurea (2i).

Benzenesulfonyl isocyanate (0.64 g, 3.48 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 50°–55° C. (22 h). The white solid (0.84 g, 66%) that separated on cooling was filtered and dried: mp 188°–191° C. (d); $R_f$ 0.11 (10% MeOH/$CHCl_3$); IR (KBr) 3250, 1630 (br), 1500 (br), 1460, 1330, 870, 700 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.80 (s, C(O)$CH_3$), 4.24 (d, J=5.7 Hz, $CH_2$), 5.47 (t, J=7.7 Hz, CH), 7.18–7.30 (m, 5PhH, NH), 7.57–7.71 (m, 3ArH), 7.89–7.92 (d, J=7.5 Hz, 2ArH), 8.54 (t, J=5.7 Hz, NH), 8.70 (d, J=7.7 Hz, NH), 10.80 (s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.29 (C(O)$CH_3$), 42.30 ($CH_2$), 57.14 (CH), 126.58 ($C_{4'}$), 126.89 ($2C_2$), 127.12 ($2C_{2'}$ or $2C_{3'}$), 128.05 ($2C_{2'}$ or $2C_{3'}$), 128.96 ($2C_3$), 133.25 ($C_4$), 138.88 ($C_1$ or $C_{1'}$), 139.87 ($C_1$ or $C_{1'}$), 150.36 (NHC(O)NH), 167.55 (C(O)NH), 169.55 (C(O)$CH_3$) ppm; mass spectrum (FD) 405 ($M^+$+1).

Anal. Calcd for $C_{18}H_{20}N_4O_5S$: C, 53.46; H, 4.98; N, 13.85. Found: C, 53.23; H, 5.04; N, 13.62.

EXAMPLE 101

Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylthiourea (2j).

A solution of 2r (0.50 g, 2.26 mmol) and methyl isothiocyanate (0.20 g, 2.27 mmol) in THF (75 mL) was heated to reflux (4 h), and then the volatile materials were removed in vacuo. The residue was recrystallized from absolute EtOH to give 2j as a white solid (0.22 g, 33%): mp 162°–163° C. (d); $R_f$ 0.45 (10% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 3220 (br), 1620, 1500, 1430, 1340, 740 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, C(O)$CH_3$), 2.85 (br s, $NHCH_3$), 4.27 (d, J=5.8 Hz, $CH_2$), 6.10 (br s, CH), 7.17–7.30 (m, 5PhH), 7.80 (br s, NH), 7.96 (br s, NH), 8.44 (br s, NH), 8.72 (s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.39 (C(O)$CH_3$), 30.92 ($NHCH_3$), 42.45 ($CH_2$), 61.33 (CH), 126.68 ($C_{4'}$) 127.06 ($2C_{2'}$ or $2C_{3'}$), 128.16 ($2C_{2'}$ or $2C_{3'}$), 139.15 ($C_{1'}$), 168.17 (C(O)NH), 170.30 (C(O)$CH_3$) ppm, the signal for the thiocarbonyl carbon group was not detected. Mass spectrum (FD) 294 ($M^+$).

Anal Calcd for $C_{13}H_{18}N_4O_2S$: C, 53.04; H, 6.16; N, 19.03. Found: C, 53.16; H, 6.31; N, 18.89.

EXAMPLE 102

Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylthiourea (2k).

A solution of 2r (0.70 g, 3.16 mmol) and phenyl isothiocyanate (0.47 g, 3.48 mmol) in THF (75 mL) was heated to reflux (3 h), and then the volatile materials were removed in vacuo. The residue was triturated with EtOH (15 mL), and the while solid material (0.70 g, 62%) that remained was filtered and recrystallized from absolute EtOH: mp 196°–197° C. (d); $R_f$ 0.65 (10% MeOH/$CHCl_3$); IR (KBr) 3400 (br, 3240 (br), 1620, 1470 (br), 1330, 750, 670 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.89 (s, C(O)$CH_3$), 4.32 (d, J=5.8 Hz, $CH_2$), 5.24 (t, J=6.9 Hz, CH), 7.09–7.43 (m, 3ArH, 5PhH), 7.52–7.55 (m, 2ArH), 8.13 (d, J=6.9 Hz, NH), 8.55 (br s, NH), 8.85 (br, s, NH), 10.11 (s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.22 (C(O)$CH_3$), 42.36 ($CH_2$), 61.18 (CH), 122.76 ($2C_2$), 124.29 ($C_4$), 126.53 ($C_{4'}$), 126.90 ($2C_{2'}$ or $2C_{3'}$), 128.00 ($2C_{2'}$ or $2C_{3'}$), 128.40 ($2C_3$), 138.94 ($C_1$ or $C_{1'}$), 139.01 ($C_1$ or $C_{1'}$), 167.82 (C(O)NH), 169.98 (C(O)$CH_3$), 180.02 (C(S)) ppm; mass spectrum (FD) 356 ($M^+$).

Anal. Calcd for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.43; H, 5.70; N, 15.62.

EXAMPLE 103

Synthesis of N-[Acetamido(benzylcarbamoyl)methyl] phthalamic acid (2l).

To a warm pyridine solution (7.0 mL) containing 2r (0.63 g, 2.83 mmol), phthalic anhydride (0.43 g, 2.87 mmol) was added, and the reaction was stirred at 50°–55° C. (5 h). Pyridine was removed by distillation in vacuo and the residue was treated with $H_2O$ (20 mL). The aqueous mixture was extracted with EtOAc (2×20 mL) and then acidified with aqueous 1N HCl solution. The white solid (0.70 g, 70%) that precipitated was filtered, washed with $H_2O$ (10 mL), and dried: mp 186°–188° C.; $^1H$ NMR (DMSO-$d_6$) δ 1.90 (s, C(O)$CH_3$), 4.36 (d, J=6.0 Hz, $CH_2$), 5.92 (t, J=7.2 Hz, CH), 7.20–7.31 (m, 5PhH), 7.43 (d, J=7.3 Hz, $C_6H$), 7.50–7.63 (m, $C_4H$, $C_5H$), 7.82 (d, J=7.3 Hz, $C_3H$), 8.41–8.48 (m, 2NH), 9.01 (d, J=7.2 Hz, NH), 13.30 (br s, $CO_2H$); $^{13}C$ NMR (DMSO-$d_6$) 22.46 (C(O)$CH_3$), 42.39 ($CH_2$), 57.44 (CH), 126.57, 126.92, 127.81, 128.09, 128.72, 129.36, 129.85, 131.49, 137.78, 138.99 (ARC, PhC), 167.85, 167.93, 168.48, 169.47 (C(O)) ppm; mass spectrum (FD) 370 ($M^+$+1).

Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.63; H, 5.05; N, 11.16.

EXAMPLE 104

Synthesis of 2-Acetamido-N-benzyl-2-(N-succinimidyl) acetamide (2m).

A cooled (–78° C.) THF solution (150 mL) of 2s[2] (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide[4,5] (2.00 g, 8.0 mmol) and $BBr_3$ (2.51 g, 10.05 mmol)) was added slowly into a cooled (–78° C.) THF suspension (50 mL) of sodium succinimide (3.06 g, 25.25 mmol). The reaction mixture was stirred at –78° C. (30 min) and at room temperature (90 min), and then treated with a 10% aqueous citric acid solution (50 mL). The resulting solution was neutralized with a saturated aqueous $NaHCO_3$ solution, and the reaction mixture extracted with EtOAc (3×100 mL). The combined extracts were dried ($Na_2SO_4$), and the volatile materials were removed by distillation in vacuo. The residue was purified by flash column chromatography on $SiO_2$ gel (6% MeOH/$CHCl_3$) to give 1.10 g (45%) of 2m: mp 1.80°–183° C. (recrystallized from EtOH);

$R_f$ 0.26 (6% MeOH/$CHCl_3$); IR (KBr) 3340 (br), 1620 (br), 1480 (br), 1340, 780, 670 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.90 (s, $C(O)CH_3$), 2.67 (s, $CH_2CH_2$), 4.23–4.36 (m, $CH_2$), 6.31 (d, J=9.0 Hz, CH), 7.17–7.35 (m, 5 PhH), 8.63 (t, J=5.9 Hz, NH), 8.72 (d, J=9.0 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.36 ($C(O)CH_3$), 27.99 (s, $CH_2CH_2$), 42.59 ($CH_2$), 55.19 (CH), 126.63 ($C_4'$), 126.96 ($2C_2'$ or $2C_3'$), 128.08 ($2C_2'$ or $2C_3'$), 138.91 ($C_1'$), 165.41 (C(O)NH), 169.86 ($C(O)CH_3$), 176.5 ($C(O)CH_2CH_2C(O)$) ppm; mass spectrum (FAB) 304 ($M^+$+1, 17), 163 (12), 155 (48), 152 (51), 135 (68), 119 (100).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.63; H, 5.70; N, 13.66.

## EXAMPLE 105

Synthesis of Benzyl N-[Acetamido(benzylcarbamoyl)methyl]malonamate (2n).

4-Methylmorpholine (0.35 g, 3.56 mmol) was added to a solution of N-CBZ-glycine (0.74 g, 3.55 mmol) in THF (75 mL) at −10° to −15° C. The solution was stirred (5 min), and then isobutyl chloroformate (0.49 g, 3.55 mmol) was added and the mixture was stirred for an additional 20 min. A cooled (−10° C.) solution of 2r (0.79 g, 3.55 mmol) in THF (125 mL) was then added slowly (30 min). The reaction mixture was stirred at this temperature (2 h) and then at room temperature (2 h). The insoluble materials were filtered and the filtrate was concentrated in vacuo. The residue was triturated with EtOAc (20 mL) and the white solid (0.60 g) that remained was filtered, washed with $H_2O$ and dried to give 2n. The initial insoluble material on trituration with $H_2O$ gave an additional 0.40 g of 2n to give a combined yield of 1.00 g (68%); mp 177°–179° C. (recrystallized from EtOH); $R_f$ 0.46 (10% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 3260, 1640 (br), 1540 (br), 1480, 1450, 1370, 760, 690 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.86 (s, $C(O)CH_3$), 3.60–3.77 (m, $C(O)CH_2NH$), 4.28 (d, J=5.8 Hz, $CH_2$), 5.01 (s, $OCH_2Ph$), 5.79 (t, J=7.7 Hz, CH), 7.18–7.34 (m, 5 PhH, 5 ArH), 7.49 (t, J=5.8 Hz, NH), 8.43–8.55 (m, 3×NH); $^{13}C$ NMR (DMSO-$d_6$) 22.36 ($C(O)CH_3$), 42.28 ($CH_2$), 43.39 ($C(O)CH_2NH$), 56.77 (CH), 65.42 ($OCH_2Ph$), 126.55 (2C), 126.94 (2C), 127.54, 127.66, 128.04 (2C), 128.22 (2C), 136.89, 138.96 (ArC, PhC), 156.40 ($NHC(O)OCH_2Ph$), 167.86 ($NHC(O)CH_2$), 168.96 (C(O)NH), 169.30 ($C(O)CH_3$) ppm; mass spectrum (FD) 413 ($M^+$+1, 100), 278 (75).

Anal. Calcd for $C_{21}H_{24}N_4O_5$: Found: C, 60.90; C, 61.16; H, 5.87; N, 1358.H, 5.77; N, 13.35.

## EXAMPLE 106

Synthesis of Ethyl N-[Acetamido(benzylcarbamoyl)methyl] glycinate (2o).

A methanolic solution (70 mL) containing 2t (1.50 g, 4.28 mmol) and ethyl glycinate (prepared from ethyl glycinate hydrochloride (3.10 g, 22.2 mmol), NaOMe (1.17 g, 21.74 mmol)) was heated to reflux (2 h). The reaction was concentrated in vacuo to give an oily residue that was purified by flash column chromatography on $SiO_2$ gel (5% MeOH/$CHCl_3$) to give 0.60 g (46%) of 29o: mp 125°–127° C. (recrystallized from EtOAc); $R_f$ 0.43 (5% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 3200, 1710, 1600, 1500, 1430, 1350, 740, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.17 (t, J=7.1 Hz, $OCH_2CH_3$), 1.86 (s, $C(O)CH_3$), 2.65–2.74 (m, $NHCH_2C(O)$), 3.26–3.33 (m, $NHCH_2C(O)$), 4.07 (q, J=7.1 Hz, $OCH_2CH_3$), 4.28 (d, J=5.8 Hz, $CH_2$), 5.01 (t, J=8.2 Hz, CH), 7.19–7.35 (m, 5 PhH), 8.25 (d, J=8.2 Hz, NH), 8.58 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 13.98 ($OCH_2CH_3$), 22.46 ($C(O)CH_3$), 42.13 ($CH_2$), 46.22 ($NHCH_2C(O)$), 60.07 ($OCH_2CH_3$), 63.96 (CH), 126.67 ($C_4'$), 127.09 ($2C_2'$ or $2C_3'$), 128.13 ($2C_2'$ or $2C_3'$), 139.07 ($C_1'$), 169.07 (C(O)NH), 170.09 ($C(O)CH_3$), 171.56 ($C(O)OCH_2CH_3$) ppm; mass spectrum (FD) 342 ($M^+$).

Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.83; H, 7.00; N, 13.73.

## EXAMPLE 107

Synthesis of Benzyl N-[Acetamido(benzylcarbamoyl)methyl]glycinate (2p).

A suspension of benzyl glycinate hydrochloride (5.00 g, 24.8 mmol) in THF (400 mL) containing $Et_3N$ (4.90 g, 48.5 mmol) was stirred (4 h) at room temperature. The reaction mixture was cooled (−78° C.) and then a cooled (−78° C.) THF solution (150 mL) of 2s (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and $BBr_3$ (1M in $CH_2Cl_2$, 20.0 mL, 20.0 mmol)) was added (30 min). The reaction mixture was stirred at −78° C. (30 min) and then at room temperature (16 h). The insoluble materials were filtered, the filtrate concentrated in vacuo, and the residue was purified by flash column chromatography on $SiO_2$ gel (3% MeOH/$CHCl_3$) to give 1.56 g (26%) of 2p as a white solid: mp 133°–135° C. (recrystallized from EtOH); $R_f$ 0.36 (3% MeOH/$CHCl_3$); IR (KBr) 3400, 3220, 1710, 1620, 1510, 1440, 1350, 740, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, $C(O)CH_3$), 2.71–2.82 (m, $NHCH_2C(O)$), 3.39 (d, J=6.1 Hz, NHCHHC(O)), 3.40 (d, J=6.1 Hz, NHCHHC(O)), 4.27 (d, J=6.1 Hz, $CH_2$), 5.02 (t, J=8.2 Hz, CH), 5.11 (s, $OCH_2Ph$), 7.19–7.36 (m, 5 PhH, 5 ArH), 8.24 (d, J=8.2 Hz, NH), 8.57 (t, J=6.1 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.42 ($C(O)CH_3$), 42.11 ($CH_2$), 46.22 ($NHCH_2C(O)$), 63.94 (CH), 65.53 ($OCH_2Ph$), 126.62, 127.05 (2C), 127.80 (2C), 127.91, 128.08 (2C), 128.29 (2C), 135.87, 139.02 (ArC, PhC), 169.01 (C(O)NH), 170.06 ($C(O)CH_3$), 171.45 (C(O)$OCH_2Ph$) ppm; mass spectrum (FD) 370 ($M^+$+1).

Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.15; H, 6.53; N, 11.31.

## EXAMPLE 108

Synthesis of N-[Acetamido(benzylcarbamoyl)methyl] glycine (2g).

A solution of methyl N-[acetamido(benzylcarbamoyl) methyl]glycinate (0.60 g, 2.05 mmol) and KOH (0.30 g, 5.36 mmol) in 90% aqueous EtOH (50 mL) was stirred at room temperature (48 h). The volatile materials were then removed in vacuo, and the residue dissolved in $H_2O$ (10 mL). The aqueous solution was extracted with EtOAc (2×20 mL), and the aqueous layer was acidified to pH −2.0 with aqueous 1N HCl. A column containing ion exchange resin Dowex 50× W4 was prepared using 10% aqueous pyridine. The column was thoroughly washed with $H_2O$. The acidic aqueous reaction solution was added to the top of the column, and the column was eluted with $H_2O$ (300 mL) or until the eluate was neutral. The column was then eluted with 10% aqueous pyridine (400 mL). The aqueous pyridine fraction was concentrated in vacuo to give a white solid, dried in vacuo, and then triturated with absolute EtOH (7 mL). The insoluble materials that remained were filtered and dried to give 0.29 g (50%) of 2q: mp 124°–126° C. (d); IR (KBr) 3400, 3200, 1630, 1500, 1370, 690 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.84 (s, $C(O)CH_3$), 3.26 (s, $CH_2C(O)$), 4.29 (d, J=5.7 Hz, $CH_2$), 4.98 (d, J=8.2 Hz, CH), 7.21–7.33 (m, NH, 5 PhH), 8.39 (d, J=8.2 Hz, NH), 8.47 (t, J=5.7 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.41 ($C(O)CH_3$), 41.98 ($CH_2$), 47.48 ($CH_2C(O)$), 64.08 (CH), 126.75 ($C_4'$), 127.21 ($2C_2'$ or $2C_3'$), 128.24 ($2C_2'$ or $2C_3'$), 139.23 ($C_1'$), 169.91 (C(O)NH), 170.02 ($C(O)CH_3$), 170.20 ($CH_2C(O)$ ppm.

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.13; N, 15.04. Found: C, 55.68; H, 6.06; N, 14.74.

EXAMPLE 109

Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole) acetamide.

A cooled (−78° C.) THF solution (225 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and $BBr_3$ (1M $CH_2Cl_2$) solution, 8.8 mL, 8.8 mmol)) was added under $N_2$ a cooled (−78° C.) suspension of potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was stirred at −78° C. (1 h) and then at room temperature (1 h), and then treated with $H_2O$ (10 mL) and acidified ("pH" 4.0) with 5% citric acid. The reaction was made basic with aqueous saturated $Na_2CO_3$ solution, and the aqueous mixture was extracted with EtOAc (2×250 mL) and the combined organic layers were dried ($Na_2SO_4$). The volatile materials were removed in vacuo and the residue was purified by flash column chromatography on $SiO_2$ gel using 3% MeOH/$CHCl_3$ as the eluant to give 0.40 g (18%) of the desired product. The compound X was purified by recrystallization from EtOH: mp 182°–184° C.; $R_f$ 0.44 (4% MeOH/$CHCl_3$); IR (KBr) 3400, 3280, 1630, 1520, 1370, 740, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.91 (s, $C(O)CH_3$), 4.30 (d, J=5.5 Hz, $CH_2$), 6.01 (s, 2×$C_3H$), 6.38 (d, J=8.7 Hz, CH), 6.85 (s, 2×$C_2H$), 7.11–7.35 (m, 5PhH), 8.96 (t, J=5.5 Hz, NH), 9.14 (d, J=8.7 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.22 ($C(O)CH_3$), 42.15 ($CH_2$), 62.86 (CH), 107.79 ($2C_3$), 119.19 ($2C_2$), 126.76 ($C_{4'}$), 127.01 ($2C_{2'}$ or $2C_{3'}$), 128.11 ($2C_{2'}$ or $2C_{3'}$), 138.34 ($C_{1'}$), 166.37 (C(O)NH), 169.41 ($C(O)CH_3$) ppm; mass spectrum, m/e (relative intensity) 272 ($M^+$+1, 22), 271 ($M^+$, 100).

Anal. Calcd for $C_{15}H_{17}N_3O_2.0.2\ H_2O$: C, 65.53; H, 6.37; N, 15.28. Found: C, 65.80; H, 6.22; N, 15.13.

EXAMPLE 110

Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole) acetamide.

To a cooled (−78° C.) solution (250 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.60 g, 14.4 mmol) and $BBr_3$ (1M $CH_2Cl_2$ solution, 15.8 mL, 15.8 mmol)), a THF solution (20 mL) of $Et_3N$ (2.91 g, 28.8 mmol) was added, followed by the addition of THF solution (30 mL) of pyrazole (1.17 g, 17.28 mmol). The mixture was stirred at −78° C. (30 min) and room temperature (1 h). The insoluble materials were filtered and the solvents removed in vacuo. The residue was purified by flash column chromatography on $SiO_2$ gel using 4% MeOH/$CHCl_3$ as the eluant to give 0.80 g (22%) of the desired product. The compound X was recrystallized from EtOAc as a white solid: mp 158°–160° C.; $R_f$ 0.51 (6% MeOH/$CHCl_3$); IR (KBr) 3400, 3180, 1650, 1530, 1470, 1370, 1350, 740, 700 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.93 (s, $C(O)CH_3$), 4.29 (d, J=5.8 Hz, $CH_2$), 6.26 (s, $C_4H$), 6.57 (d, J=8.8 Hz, CH), 7.15–7.33 (m, 5PhH), 7.48 (br s, $C_5H$), 7.76 (br s, $C_3H$), 8.96 (t, J=5.8 Hz, NH), 9.23 (d, J=8.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.41 ($C(O)CH_3$), 42.40 ($CH_2$), 65.51 (CH), 105.37 ($C_4$), 126.87 ($C_{4'}$), 127.14 ($2C_{2'}$ or $2C_{3'}$), 128.25 ($2C_{2'}$ or $2C_{3'}$), 129.00 ($C_5$), 138.59 ($C_3$), 139.17 ($C_{1'}$), 165.68 (C(O)NH), 169.81 ($C(O)CH_3$) ppm; mass spectrum, m/e (relative intensity) 273 ($M^+$+1, 11), 272 ($M^+$, 2), 139 (83), 138 (100), 92 (37).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 5.96; N, 20.28.

EXAMPLE 111

Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole) acetamide.

Using the preceeding procedure, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 8.8 mL, 8.8 mmol), $Et_3N$ (1.62 g, 1.60 mmol), and imidazole (0.60 g, 8.8 mmol) gave 0.60 g (30%) of the desired product. Compound X was recrystallized from ethyl acetate/hexane as a beige colored solid: mp 146°–148° C.; $R_f$ 0. (7% MeOH/$CHCl_3$); IR (KBr) 3400 (br), 1640, 1560, 1480, 1360, 720, 670 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, $C(O)CH_3$), 4.30 (br s, $CH_2$), 6.53 (d, J=8.0 Hz, CH), 6.89 (s, $C_5H$), 7.12–7.33 (m, $C_4H$, 5PhH), 7.69 (s, $C_2H$), 9.06 (br s, NH), 9.29 (d, J=8.0 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.28 ($C(O)CH_3$), 42.36 ($CH_2$) 61.18 (CH), 117.56 ($C_5$), 126.92 ($C_{4'}$), 127.16 ($2C_{2'}$ or $2C_{3'}$), 128.19 ($C_4$), 128.26 ($2C_{2'}$ or $2C_{3'}$), 136.21 ($C_2$), 138.27 ($C_{1'}$), 165.72 (C(O)NH), 169.77 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 274 ($M^+$+2, 12), 273 ($M^+$+1, 77), 272 (100), 205 (34) 274 (18).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95; H, 6.09; N, 20.32.

EXAMPLE 112

Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole)) acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 17.6 mL, 17.6 mmol), $Et_3N$ (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g, 20.8 mmol), 1.20 g (28%) of the desired product was obtained. Compound X was recrystallized from EtOAc as an amorphous white solid: mp 146°–148° C.; $R_f$ 0.48 (6% MeOH/$CHCl_3$); IR (KBr) 3400, 1660, 1470, 1370, 830 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.85 (s, $C(O)CH_3$), 4.32 (br s, $CH_2$), 6.70 (d, J=7.8 Hz, CH), 7.21–7.29 (m, 5PhH), 8.01 (s, $C_3H$), 8.57 (s, $C_5H$), 9.04 (br s, NH), 9.39 (d, J=7.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.39 ($C(O)CH_3$), 42.59 ($CH_2$), 65.02 (CH), 126.97 ($C_{4'}$), 127.25 ($2C_{2'}$ or $2C_{3'}$), 128.32 ($2C_{2'}$ or $2C_{3'}$), 138.47 ($C_{1'}$), 143.93 ($C_5$), 151.50 ($C_3$), 164.77 (C(O)NH), 170.23 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 274 ($M^+$+1, 100), 273 (11), 205 (19), 204 (13), 140 (67), 139 (31).

Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37; H, 5.66; N, 25.38.

EXAMPLE 113

Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole)) acetamide.

Making use of 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), $BBr_3$ (1M $CH_2Cl_2$ solution, 13.2 mL, 13.2 mmol), $Et_3N$ (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6 mmol), 0.90 g (27%) of the desired product was obtained as a white solid. The compound X was recrystallized from EtOH: mp 169°–171° C.; $R_f$ 0.22 (4% MeOH/$CHCl_3$); IR (KBr) 3300 (br), 1660, 1510, 1360, 870, 740 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.97 (s, $C(O)CH_3$), 4.25–4.40 (m, $CH_2$), 7.05 (d, J=8.4 Hz, CH), 7.21–7.38 (m, 5PhH), 9.23 (t, J=5.5 Hz, NH), 9.44 (s, $C_5H$), 9.69 (d, J=8.4 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.38 ($C(O)CH_3$), 42.78 ($CH_2$), 63.62 (CH), 127.10 ($C_{4'}$), 127.39 ($2C_{2'}$ or $2C_{3'}$), 128.38 ($2C_{2'}$ or $2C_{3'}$), 138.26 ($C_{1'}$), 143.67 ($C_5$), 163.88 (C(O)NH), 170.62 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 275 ($M^+$, 79), 273 (14), 206 (100), 205 (50).

Anal. Calcd for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75; H, 5.33; N, 30.64.

EXAMPLE 114

Synthesis of α-Acetamido-N-benzyl-1-(dimethylsulfamoyl) imidazole-4-acetamide.

To a cooled (–78° C.) THF solution (150 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and $BBr_3$ (1M solution in $CH_2Cl_2$, 9.0 mL, 9.0 mmol)) was added $Et_3N$ (1.62 g, 16.0 mmol), and then a THF solution of the 2-lithio salt of N,N-dimethylimidazole-1-sulfonamide (generated by the addition of n-BuLi (2.5M in hexane, 3.9 mL, 9.68 mmol) into a cooled (–78° C.) THF solution (25 mL) of N,N-dimethylimidazole-1-sulfonamide (1.54 g, 8.8 mmol)) was added during a 15 min interval. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (45 min). A saturated aqueous $NH_4Cl$ solution (50 mL) and $H_2O$ (50 mL) were then sucessively added to the reaction, and the aqueous mixture was extracted with EtOAc (3×50 mL). The combined extracts were dried ($Na_2SO_4$), and the volatile materials were removed by distillation in vacuo. The residue was purified by flash column chromatography on $SiO_2$ gel (4% MeOH/$CHCl_3$) to give 0.50 g (17%) of the desired product: mp 145°–147° C. (recrystallized from EtOAc/hexane); $R_f$ 0.35 (4% MeOH/$CHCl_3$); IR (KBr) 3400, 1640, 1530, 1380, 720 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.96 (s, $C(O)CH_3$), 2.77 (s, $N(CH_3)_2$), 4.25 (dd, J=6.0, 15.5 Hz, CHH), 4.34 (dd, J=6.0, 15.5 Hz, CHH), 5.43 (d, J=8.0, Hz, CH), 7.19–7.30 (m, 5 PhH), 7.40 (s, $C_5H$), 8.17 (s, $C_2H$), 8.42 (d, J=8.0 Hz, NH), 8.67 (t, J=6.0 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.42 ($C(O)CH_3$), 37.80 ($N(CH_3)_2$), 42.11 ($CH_2$), 51.40 (CH), 115.50 ($C_5$), 126.64 ($C_{4'}$), 126.94 ($2C_{2'}$ or $2C_{3'}$), 128.12 ($2C_{2'}$ or $2C_{3'}$), 136.70 ($C_2$), 139.17 ($C_{1'}$), 140.26 ($C_4$), 168.93 (C(O)NH), 169.09 ($C(O)CH_3$) ppm; mass spectrum (FD) 380 ($M^+$+1, 34), 248 (13), 247 (100), 108 (64).

Anal. Calcd for $C_{16}H_{21}N_5O_4S$: C, 50.65; H, 5.58; N, 17.87. Found: C, 51.92; H, 5.65; N, 18.09.

## EXAMPLE 115

Synthesis of α-Acetamido-N-benzyl-4-imidazole acetamide.

A 75% aqueous EtOH (16 mL) solution of α-acetamido-N-benzyl-1-(N,N-dimethylsulfamido)imidazole-4-acetamide (0.85 g, 3.05 mmol) was acidified ("pH" ~1.5) with ethanolic HCl, and the solution was heated to reflux (8 h). The reaction was neutralized with a saturated aqueous $NaHCO_3$ solution and the EtOH-$H_2O$ azeotrope removed by distillation in vacuo. The remaining aqueous layer was made basic ("pH" 10) with aqueous NaOH. The aqueous mixture was extracted with EtOAc (3×50 mL) and the combined extracts were dried ($Na_2SO_4$). The reaction was concentrated in vacuo to give 0.35 g (57%) of the desired product: mp 189°–191° C. (d) (recrystallized from acetone); $R_f$ 0.19 (10% MeOH/$CHCl_3$); IR (KBr) 3400, 3260, 1650, 1600, 1500, 1430, 1360, 1330, 730, 710 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.88 (s, $C(O)CH_3$), 4.28 (d, J=5.9 Hz, $CH_2$), 5.38 (d, J=6.8 Hz, CH), 5.38 (br s, $C_5H$), 7.15–7.30 (m, 5 PhH), 7.60 (s, $C_2H$), 8.26 (br s, NH), 8.53 (br s, NH), 12.01 (br s, NH) ppm; mass spectrum (FD) 273 ($M^+$+1).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.59; H, 5.98; N, 20.37.

## EXAMPLE 116

Synthesis of α-Acetamido-N-benzyl-2-imidazole acetamide.

Preparation or 1-diethoxymethyl-2-lithioimidazole.

n-BuLi (2.5M in hexane, 6.8 mL, 17.0 mmol) was added to a cooled (–46° C.) solution of 1-diethoxymethylimidazole (2.90 g, 17.06 mmol) in THF (45 mL) under $N_2$ atm. The solution was stirred at –46° C. (15 min) to give the desired product.

Preparation of α-Acetamido-N-benzyl-2-imidazoleacetamide.

The 2-lithio salt solution of 1-diethoxymethylimidazole was added dropwise (15 min) into a cooled (–78° C.) THF solution (130 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and $BBr_3$ (1M in $CH_2Cl_2$, 10 mL, 10.0 mmol)). The reaction was stirred at –78° C. (1 h) and then quenched with a saturated aqueous $NH_4Cl$ (50 mL) solution. The mixture was stirred at room temperature (30 min), and made basic ("pH" 9.2)by adding aqueous $K_2CO_3$. The aqueous mixture was extracted with EtOAc (3×100 mL), and the combined extracts were dried ($Na_2SO_4$). The solvents were removed in vacuo and the residue was purified by flash column chromatography on $SiO_2$ gel (2.5% MeOH/$CHCl_3$) to give 0.14 g (7%) of the desired product: mp 228°–230° C. (recrystallized from EtOH); $R_f$ 0.46 (10% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 1610, 1500 (br), 1430, 1350, 740, 680 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.91 (s, $C(O)CH_3$), 4.29 (d, J=5.6 Hz, $CH_2$), 5.51 (d, J=7.7 Hz, CH), 6.85 (br s, $C_4H$), 7.05 (br s, $C_5H$), 7.18–7.30 (m, 5 PhH), 8.42 (d, J=7.7 Hz, NH), 8.65 (t, J=5.6 Hz, NH), 11.91 (br s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.49 ($C(O)CH_3$), 42.21 ($CH_2$), 51.62 (CH), 126.60 ($C_{4'}$), 126.98 ($2C_{2'}$ or $2C_{3'}$), 127.21 ($C_4$), 128.09 ($2C_{2'}$ or $2C_{3'}$), 128.32 ($C_5$), 139.05 ($C_{1'}$), 143.74 ($C_2$), 168.12 (C(O)NH), 169.30 ($C(O)CH_3$) ppm; mass spectrum (FD) 273 ($M^+$+1, 65), 272 ($M^+$, 100).

Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.56; H, 5.92; N, 20.37.

## EXAMPLE 117

Synthesis of α-Acetamido-N-benzyl-5-(tetrazole) acetamide.

A mixture of (2-acetamido-N-benzyl-2-cyanoacetamide (1.00 g, 4.33 mmol), potassium azide (1.70 g, 20.96 mmol) and $Et_3N$.HCl (1.78 g, 13.0 mmol) in 1-methyl-2-pyrrolidinone (1.25 mL) was stirred at 110° C. (7 h). After cooling, aqueous concentrated HCl (1 mL) was added, and the reaction mixture was filtered. The solvent was removed in vacuo. The residue was dissolved in aqueous 1N NaOH (20 mL), and then aqueous 1N HCl (20 mL) was added. The precipitate was filtered to give 0.77 g (65%) of the desired product. The compound X was recrystallized from EtOH: mp 236°–238° C.; $R_f$ 0.20 (30% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.94 (s, $C(O)CH_3$), 4.33 (d, J=5.7 Hz, $CH_2$), 5.89 (d, J=7.8 Hz, CH), 7.18–7.33 (m, 5 PhH), 8.86 (d, J=7.8 Hz, NH), 8.92 (t, J=5.7 Hz, NH), 16.54 (br s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.21 ($C(O)CH_3$), 42.37 ($CH_2$), 48.13 (CH), 126.67 ($C_{4'}$), 127.00 ($2C_{2'}$ or $2C_{3'}$), 128.05 ($2C_{2'}$ or $2C_{3'}$), 138.52 ($C_{1'}$), 166.18 (C(O)NH), 169.58 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 275 ($M^+$+1, 73), 274 (100). $M_r$ (+CI) 274.119201 (calcd for $C_{12}H_{14}N_6O_2$: 274.117824.

## EXAMPLE 118

Synthesis of α-Acetamido-N-benzyl-3-(1,2,4-triazole) acetamide.

An ethanolic solution (250 mL) of 2-acetamido-N-benzyl-2-cyanoacetamide (3.00 g, 13.0 mmol), formic hydrazide (1.60 g, 26.0 mmol) and $K_2CO_3$ (6.00 g, 2.90 mmol) was heated at reflux (20 h). The reaction mixture was allowed to cool, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on $SiO_2$ gel using 13% MeOH/$CHCl_3$ as the eluant to give 1.40 g (40%) of the desired product. The compound

X was purified by recrystallization from EtOH: mp 205°–207° C.; $R_f$ 0.35 (16% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.92 (s, $C(O)CH_3$), 4.30 (d, J=5.7 Hz, $CH_2$), 5.62 (d, J=7.8 Hz, CH), 7.18–7.32 (m, 5 PhH), 8.53 (s, $C_5H$), 8.56 (d, J=7.8 Hz, NH), 8.71 (t, J=5.7 Hz, NH), 13.98 (s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.48 ($C(O)CH_3$), 42.41 ($CH_2$), 51.30 (CH), 126.63 ($C_{4'}$), 127.08 ($2C_{2'}$ or $2C_{3'}$), 128.11 ($2C_{2'}$ or $2C_{3'}$), 139.05 ($C_{1'}$), 167.92 (C(O)NH), 169.32 ($C(O)CH_3$); ppm; mass spectrum, FD (relative intensity) 274 ($M^+$+1, 100), 273 (66).

Anal. Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.32; H, 5.57; N, 25.53.

## EXAMPLE 119

Synthesis of α-Acetamido-N-benzyl-2-(carboxamide oxime)acetamide.

A suspension of $NH_2OH.HCl$ (1.80 g, 25.9 mmol), $K_2CO_3$ (4.85 g, 35.0 mmol), 2-acetamido-N-benzyl-2-cyanoacetamide (2.00 g, 8.65 mmol) in absolute EtOH (150 mL) was heated at reflux (16 h). The reaction mixture was cooled, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on $SiO_2$ gel using 8% MeOH/$CHCl_3$ as the eluant to give 1.24 g (54%) of the desired product. The compound X was further purified by recrystallization from ethyl acetate/hexane: mp 172°–173° C.; $R_f$ 0.40 (10% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.87 (s, $C(O)CH_3$), 4.27 (d, J=6.0 Hz, $CH_2$), 4.88 (d, J=8.4 Hz, CH), 5.37 (s, $NH_2$), 7.21–7.30 (m, 5 PhH), 8.21 (d, J=8.4 Hz, NH), 8.48 (t, J=6.0 Hz, NH), 9.28 (s, OH); $^{13}C$ NMR (DMSO-$d_6$) 22.46 ($C(O)CH_3$), 42.15 ($CH_2$), 53.65 (CH), 126.60 ($C_{4'}$), 126.99 ($2C_{2'}$ or $2C_{3'}$), 128.108 ($2C_{2'}$ or $2C_{3'}$), 139.02 ($C_{1'}$), 149.63 ($CNH_2$), 167.88 (C(O)NH), 169.07 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 265 ($M^+$+1, 36), 264 (100).

Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.81; H, 6.01; N, 21.41.

## EXAMPLE 120

Synthesis of α-Acetamido-N-benzyl-2-(carboxamide oxime-(O-acetate))acetamide.

To a stirred solution of α-acetamido-N-benzyl-2-(carboxamide oxime)acetamide (0.72 g, 7.25 mmol) in pyridine (8 mL), acetyl chloride (0.25 mL, X mmol) was added dropwise. Upon addition of the acetyl chloride a small exotherm was detected (25° C. to 37° C.). The reaction mixture was stirred at room temperature (1 h). The solvent was then removed in vacuo, and the residue was dissolved in $CH_2Cl_2$ (100 mL). The solution was washed with an aqueous 0.5N HCl solution (20 mL). The organic phase was dried ($Na_2SO_4$), and the solvent was removed in vacuo to give 0.60 g (72%) of the desired product. The compound X was recrystallized from chloroform/hexane: mp 131°–133° C.; $R_f$ 0.35 (4% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.90 (s, $C(O)CH_3$), 2.06 (s, $OC(O)CH_3$), 4.29 (t, J=5.3 Hz, $CH_2$), 5.00 (d, J=8.4 Hz, CH), 6.48 (br s, $NH_2$), 7.19–7.33 (m, 5 PhH), 8.29 (d, J=8.4 Hz, NH), 8.66 (t, J=5.3 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 19.86 ($OC(O)CH_3$), 22.77 ($C(O)CH_3$), 42.50 ($CH_2$), 53.45 (CH), 126.89 ($C_{4'}$), 127.28 ($2C_{2'}$ or $2C_{3'}$), 128.38 ($2C_{2'}$ or $2C_{3'}$), 139.00 ($C_{1'}$), 156.13 ($CNH_2$), 167.19 (C(O)NH), 168.49 ($OC(O)CH_3$), 169.55 ($C(O)CH_3$) ppm; mass spectrum, FD (relative intensity) 307 ($M^+$+1, 100), 306 (43).

Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.86; H, 5.84; N, 18.19.

## EXAMPLE 121

Synthesis of α-Acetamido-N-benzyl-3-(1,2,4-oxadiazole) acetamide.

α-Acetamido-N-benzyl-2-(carboxamide oxime) acetamide (0.90 g, 3.4 mmol) was dissolved in trimethylorthoformate (10 mL) containing $BF_3.Et_2O$ (6 drops). The solution was warmed to 55° C. (20 min), and then evaporated under reduced pressure to give a white-blue solid. The material was dissolved in MeOH and treated with norit, filtered, and evaporated under reduced pressure to furnish crude product (0.79 g, 85%). The compound was purified by recrystallization from chloroform/hexane: mp 164°–166° C.; $R_f$ 0.37 (6% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.92 (s, $C(O)CH_3$), 4.31 (d, J=6.0 Hz, $CH_2$), 5.82 (d, J=8.4 Hz, CH), 7.15–7.34 (m, 5 PhH), 8.88 (d, J=8.4 Hz, NH), 8.96 (t, J=6.0 Hz, NH), 9.62 (s, $C_5H$); $^{13}C$ NMR (DMSO-$d_6$) 22.22 ($C(O)CH_3$), 42.35 ($CH_2$), 49.44 (CH), 126.77 ($C_{4'}$), 127.06 ($2C_{2'}$ or $2C_{3'}$), 128.18 ($2C_{2'}$ or $2C_{3'}$), 138.70 ($C_{1'}$), 166.25 (C(O)NH), 166.74 ($C_3$), 167.24 ($C(O)CH_3$), 169.52 ($C_5$, CH) ppm; mass spectrum, FD (relative intensity) 275 ($M^+$+1, 28), 274 (100).

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.65; H, 5.01; N, 20.28.

## EXAMPLE 122

Synthesis of α-Acetamido-N-benzyl-2-(thioamide) acetamide.

2-Acetamido-N-benzyl-2-cyanoacetamide (4.00 g, 34.64 mmol) and O,O-diethyldithiophosphoric acid (6.45 g, 34.64 mmol) were dissolved in a binary MeOH (80 mL)-EtOH (80 mL) solution containing $H_2O$ (0.32 mL) and heated at 70° C. (6 h) and then allowed to remain at room temperature (13 h). The reaction mixture was filtered, and the solvent was removed in vacuo. The residue was triturated with EtOAc to give 2.00 g (44%) of the desired compound. The thioamide was recrystallized from ethyl acetate/hexane: mp 170°–171° C.; $R_f$ 0.51 (8% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.93 (s, $C(O)CH_3$), 4.29 (d, J=5.0 Hz, $CH_2$), 5.21 (d, J=8.0 Hz, CH), 7.15–7.31 (m, 5 PhH), 8.03 (d, J=8.0 Hz, NH), 8.69 (t, J=5.0 Hz, NH), 9.27 (s, NHH'), 9.91 (s, NHH); $^{13}C$ NMR (DMSO-$d_6$) 22.68 ($C(O)CH_3$), 42.24 ($CH_2$), 62.95 (CH), 126.63 ($C_{4'}$), 126.96 ($2C_{2'}$ or $2C_{3'}$), 128.087 ($2C_{2'}$ or $2C_{3'}$), 138.83 ($C_{1'}$), 166.42 (C(O)NH), 169.10 ($C(O)CH_3$), 200.28 ($C(S)NH_2$) ppm; mass spectrum, FD (relative intensity) 266 ($M^+$+1, 42), 265 (100).

Anal. Calcd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.44; H, 5.74; N, 15.54.

## EXAMPLE 123

Synthesis of Ethyl 2-Acetamido-2-vinylacetate.

Vinyl magnesium bromide (10.9 mL, 1N, 10.9 mmol) was slowly added to a cooled (–78° C.) solution of ethyl 2-acetamido-2-bromoacetate (1.10 g, 4.91 mmol) in THF (50 mL). The reaction was stirred at –78° C. (2 h), and was then quenched with a 1N citric acid solution (7.0 mL). The mixture was allowed to warm to room temperature, and then the THF was removed in vacuo. The aqueous mixture was extracted with $CHCl_3$ (3×100 mL), and the combined $CHCl_3$ extracts were dried ($Na_2SO_4$) and concentrated to dryness. The residue was purified by flash chromatography using $SiO_2$ gel and 2% MeOH/$CHCl_3$ as the eluant to give 0.50 g (60%) of the desired product as a light yellow colored oil: $R_f$ 0.51 (4% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.17 (t, J=7.1 Hz, $OCH_2CH_3$), 1.88 (s, $C(O)CH_3$), 4.09 (d, J=7.1 Hz, $OCH_2CH_3$), 4.80–4.86 (m, α-CH), 5.22–5.35 (m, $CH{=}CH_2$), 5.82–5.92 (m, $CH{=}CH_2$), 8.47 (d, J=7.4 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 13.96 ($OCH_2CH_3$), 22.12 ($C(O)CH_3$), 54.65 (α-CH), 60.71 ($OCH_2CH_3$), 117.89 ($CH{=}CH_2$), 132.48 ($CH{=}CH_2$), 169.16 ($C(O)CH_3$), 170.26 (C(O)NH) ppm.

EXAMPLE 124

Synthesis of Vinyl Glycine.

A mixture of ethyl 2-acetamido-2-vinyl acetate (5.20 g, 30.40 mmol) and aqueous 6N HCl (200 mL) was heated to reflux (2 h). The mixture was cooled to room temperature, and then extracted with $CHCl_3$ (3×100 mL). The aqueous solution which was dark brown in color was decolorized with norit (15 min) at. 60° C., and then the mixture was filtered, and the filtrate was concentrated to dryness to give aude vinyl glycine hydrochloride. The salt was dissolved in a minimum amount of $H_2O$ and acidified to pH 2.0 with aqueous 1N HCl. The solution was applied to an ion exchange resin (Dowex 50XW4, ammonium form) and eluted with $H_2O$ until the eluate was neutral. The ion exchange column was then eluted with an aqueous 1N $NH_4OH$ solution (~500 mL). Removal of volatile materials from the $NH_4OH$ eluate gave 1.80 g (60%) of vinyl glycine: mp 218°–220° C. (d); $^1H$ NMR ($D_2O$) δ 4.09 (d, J=7.2 Hz, α-CH), 5.28–5.35 (m, $CH=CH_2$), 5.80–5.87 (m, $CH=CH_2$).

EXAMPLE 125

Synthesis of 2-Acetamido-2-vinylacetic acid.

Acetic anhydride (2.50 g, 24.50 mmol) was added slowly into a cooled (−10° C.) solution of vinyl glycine (2.20 g, 21.78 mmol) in AcOH (100 mL). The mixture was stirred at this temperature (30 min) and then at room temperature (3 h). The solution was concentrated repeatedly from $H_2O$. The residue was dissolved in absolute EtOH (200 mL) and then decolorized (norit, 60° C.), and filtered. The filtrate was concentrated in vacuo, and the residue was triturated with $Et_2O$ to give 1.70 g (55%) of the desired product as a low melting yellow solid: $^1H$ NMR (DMSO-$d_6$) δ 1.87 (s, $C(O)CH_3$), 4.75 (dd, J=6.2, 7.5 Hz, α-CH), 5.13–5.27 (m, $CH=CH_2$), 5.84–5.96 (m, $CH=CH_2$), 8.24 (d, J=7.5 Hz, NH).

EXAMPLE 126

Synthesis of 2-Acetamido-N-benzyl-2-vinylacetamide.

4-Methylmorpholine (0.71 g, 6.99 mmol) was added to a suspension of 2-acetamido-2-vinylacetic acid (1.00 g, 6.99 mmol) in THF (325 mL), and the mixture was stirred at room temperature (30 min). The reaction was cooled to −10° to −15° C. and then isobutylchloroformate (1.24 g, 9.08 mmol) was then added dropwise. After stirring (10 min), a solution of benzylamine (0.75 g, 6.99 mmol) in THF (25 mL) was added (15 min). The reaction mixture was allowed to warm to 0° C. The insoluble material was filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on $SiO_2$ gel using 3% MeOH/$CHCl_3$ as the eluant to give 1.00 g (62%) of the desired product: mp 136°–138° C. (recrystallized from EtOAc); $R_f$ 0.24 (3% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.88 (s, $C(O)CH_3$), 4.27 (d, J=5.6 Hz, $CH_2$), 4.89–4.94 (dd, J=6.4, 7.8 Hz, α-CH), 5.13–5.30 (m, —$CH=CH_2$), 5.81–5.93 (m, —$CH=CH_2$), 7.20–7.33 (m, 5 PhH), 8.27 (c, J=7.8 Hz, NH), 8.58 (t, J=5.6 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.47 ($C(O)CH_3$), 42.05 ($CH_2$), 55.24 (α-CH), 116.44 ($CH=CH_2$), 126.74 ($C_{4'}$), 127.05 ($2C_{2'}$ or $2C_{3'}$), 128.24 ($2C_{2'}$ or $2C_{3'}$), 134.76 ($CH=CH_2$), 139.25 ($C_{1'}$), 168.78 ($C(O)CH_3$), 168.99 (C(O)NH) ppm.

EXAMPLE 127

Synthesis of 2-Acetamido-N-benzyl-2-epoxyacetamide.

A solution of 2-acetamido-N-benzyl-2-vinylacetamide (1.00 g, 4.31 mmol) and m-chloroperoxybenzoic acid (1.76 g, 55%, 5.60 mmol) in dichloromethane (100 mL) was stirred at room temperature (24 h), and then heated at reflux (3 h). The reaction solution was treated with a saturated aqueous $Na_2SO_3$ solution (20 mL) and then the organic layer was extracted with a saturated aqueous $NaHCO_3$ solution (3×50 mL). The organic layer was washed with a saturated aqueous NaCl solution and dried ($Na_2SO_4$). The $CH_2Cl_2$ was removed in vacuo, and the residue was then purified by flash column chromatography on $SiO_2$ gel using 4% MeOH/EtOAc as the eluant to give 0.35 g (33%) of the desired product: mp °C. (recrystallized from EtOAc); $R_f$ 0.48 (5% MeOH/$CHCl_3$); $^1H$ NMR (DMSO-$d_6$) δ 1.87 (s, $C(O)CH_3$), 2.66 (dd, J=2.5, 5.0 Hz, CH(O)CHH), 2.75 (dd, J=4.3, 5.0 Hz, CH(O)CHH), 3.20 (m, CH(O)CHH), 4.25–4.32 (m, α-CH, $CH_2$), 7.21–7.34 (m, 5 PhH), 8.30 (d, J=8.1 Hz, NH), 8.59 (t, J=5.8 Hz, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.18 ($C(O)CH_3$), 41.99 ($CH_2$), 43.91 ($CH(O)CH_2$), 51.30 ($CH(O)CH_2$), 53.80 (α-CH), 126.49 ($C_{4'}$), 126.83 ($2C_{2'}$ or $2C_{3'}$), 127.98 ($2C_{2'}$ or $2C_{3'}$), 138.86 ($C_{1'}$), 168.52 (C(O)NH), 169.24 ($C(O)CH_3$) ppm.

EXAMPLE 128

Synthesis of Potassium 2-Acetamido-N-benzylacetamide-2-sulfonate.

A solution of 2-acetamido-N-benzyl-2-(trimethylammonium)acetamide tetrafluoroborate (0.30 g, 0.85 mmol) and $K_2SO_3$ (0.68 g, 4.26 mmol) in $H_2O$ (7.0 mL) was heated at 50°–55° C. (4 h). The solution was evaporated to dryness, and the residue was extracted with hot MeOH (3×10 mL). The MeOH was removed in vacuo to give a white solid (~30 mg): $^1H$ NMR ($D_2O$) δ 1.97 (s, $C(O)CH_3$), 4.33 ($CH_2$), 5.45 (CH), 7.19–7.28 (m, 5 PhH); $^{13}C$ NMR ($D_2O$) 22.00 ($C(O)CH_3$), 43.41 ($CH_2$), 67.77 (CH), 127.18 ($2C_{2'}$ or $2C_{3'}$), 127.53 ($C_{4'}$), 128.83 ($2C_{2'}$ or $2C_{3'}$), 137.58 ($C_{1'}$), 166.02 (C(O)NH), 173.65 ($C(O)CH_3$) ppm.

EXAMPLE 129

Synthesis of Ethyl 2-Acetamido-4-pentenoic acid ester.

Allyltrimethylsilane (4.09 g, 31.40 mmol) was added to a stirred solution of ethyl 2-acetamido-2-bromoacetate (1.76 g, 7.86 mmol) in dry THF (90 mL). After stirring (5 min), an ethereal solution of $ZnCl_2$ (1N, 12.2 mL, 12.2 mmol) was added and the stirring was continued (70 h). The THF was removed by distillation in vacuo and the residue that remained was treated with $H_2O$ (50 mL). The aqueous mixture was extracted with $CH_2Cl_2$ (3×75 mL), the combined extract was dried ($Na_2SO_4$) and concentrated to give 1.40 g (97%) of the desired product. The ester was purified by distillation in vacuo (65°–70° C., 0.3–0.8 torr) to give the desired product as a colorless oil: $R_f$ 0.35 (3% MeOH/$CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.25 (t, J=6.8 Hz, $OCH_2CH_3$), 1.99 (s, $C(O)CH_3$), 2.44–2.60 (m, $CH_2CH=CH_2$), 4.17 (q, J=6.8 Hz, $OCH_2CH_3$), 4.60–4.66 (m, CH), 5.07–5.11 (m, $CH_2CH=CH_2$), 5.59–5.70 (m, $CH_2CH=CH_2$), 6.15 (br s, NH); $^{13}C$ NMR ($CDCl_3$) 14.09 ($OCH_2CH_3$), 23.00 ($C(O)CH_3$), 36.46 ($CH_2CH=CH_2$), 51.58 (CH), 61.39 ($OCH_2CH_3$), 118.95 ($CH_2CH=CH_2$), 132.15 ($CH_2CH=CH_2$), 169.64 ($C(O)CH_3$), 171.74 (C(O)$OCH_2CH_3$) ppm; mass spectrum, m/e (relative intensity) 186 ($M^+$+1, 2), 144 (19), 126 (7), 112 (31), 102 (73), 87 (18), 71 (100), 70 (89).

EXAMPLE 130

Synthesis of 2-Acetamido-4-pentenoic acid.

Ethyl 2-acetamido-4-pentenoic acid ester (1.20 g, 6.50 mmol) was dissolved in 90:5 EtOH:$H_2O$ (40 mL), and then

KOH (1.50 g, 26.80 mmol) was added and the resulting solution stirred at room temperature (48 h). The reaction was concentrated in vacuo and the residue diluted with $H_2O$ (15 mL) and then washed with $Et_2O$ (2×30 mL). The aqueous layer was then made acidic with 8.5% $H_3PO_4$ and extracted with EtOAc (3×75 mL). The combined organic layers were dried ($Na_2SO_4$), and evaporated in vacuo to give 0.56 g (55%) of the desired product: mp 113°–115° C. (recrystallized from EtOAc); $^1H$ NMR (DMSO-$d_6$) δ 2.00 ($C(O)CH_3$), 2.43–2.65 (m, $CH_2CH=CH_2$), 4.36–4.43 (m, CH), 5.19–5.30 (m, $CH_2CH=CH_2$), 5.84–5.98 (m, $CH_2CH=CH_2$), 8.29 (d, J=7.7 Hz, NH), 12.78 (br s, OH); $^{13}C$ NMR (DMSO-$d_6$) 22.35 ($C(O)CH_3$), 35.44 ($CH_2CH=CH_3$), 51.68 (CH), 117.70 ($CH_2CH=CH_2$), 134.07 ($CH_2CH=CH_2$), 169.27 ($C(O)CH_3$), 173.11 ($CO_2H$) ppm; mass spectrum, m/e (relative intensity) 158 ($M^+$+1, 2), 139 (6), 116 (20), 112 (8), 74 (73), 70 (47), 42 (100).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.06; N, 8.91. Found: C. 53.64; H, 7.15; N, 8.82.

## EXAMPLE 131

Synthesis of 2-Acetamido-4-pentenoic acid-N-benzylamide.

4-Methylmorpholine (0.55 g, 5.40 mmol) was added to a cooled (−10° to −15° C.) THF solution (60 mL) of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol), and then isobutylchloroformate (0.75 g, 5.70 mmol) was added leading to the precipitation of a white solid. After 2 min, a solution of benzylamine (0.61 g, 5.70 mmol) in THF (10 mL) was slowly added at −10° to −15° C. The reaction was allowed to warm (5 min) at room temperature and the insoluble salts were removed by filteration, and the filtrate was evaporated to dryness. The residue was triturated with EtOAc (10 mL), and the remaining white solid was filtered to give 0.81 g (64%) of the desired product: mp 118°–120° C. (recrystallized from ethyl acetate/cyclohexane); $R_f$ 0.36 (4% MeOH/$CHCl_3$); IR (KBr) 3200 (br), 3040, 2900, 1650 (br), 1540 (br), 1350, 750, 700 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) δ 1.83 (s, $C(O)CH_3$), 2.22–2.49 (m, $CH_2CH=CH_2$), 4.26 (d, J=5.3 Hz, $CH_2Ph$), 4.25–4.33 (m, CH), 4.99–5.09 (m, $CH_2CH=CH_2$), 5.65–5.77 (m, $CH_2CH=CH_2$), 7.21–7.29 (m, 5 PhH), 8.05 (d, J=7.6 Hz, NH), 8.46 (br s, NH); $^{13}C$ NMR (DMSO-$d_6$) 22.41 ($C(O)CH_3$), 36.24 ($CH_2CH=CH_2$), 41.91 ($CH_2Ph$), 52.20 (CH), 117.15 ($CH_2CH=CH_2$), 126.54 ($C_{4'}$), 126.99 ($2C_{2'}$ or $2C_{3'}$), 128.04 ($2C_{2'}$ or $2C_{3'}$), 139.25 ($C_{1'}$), 134.25 ($CH_2CH=CH_2$), 169.02 ($C(O)CH_3$), 170.96 (C(O)NH) ppm; mass spectrum, m/e (relative intensity) 246 ($M^+$, 4), 205 (4), 163 (15), 140 (8), 106 (33), 91 (77), 70 (100).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.55; H, 7.31; N, 11.48.

## EXAMPLE 132

Using the procedures described herein, the following compounds can also be synthesized:
α-acetamido-N-benzyl-2-(2-oxazole)-acetamide
α-acetamido-N-benzyl-2-(2-thiazole)-acetamide.

Pharmacology.

Using male Carworth Farms #1 mice, compounds of the present invention were tested for anticonvulsant activity according to the following procedure: In the rotorod test, the animal was placed on a one-inch diameter knurled plastic rod rotating at 6 rpm after the administration of the drug. Normal mice can remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for one minute. In the horizontal screen test, previously trained mice were dosed with the compound and placed individually on top of a square (13 cm×13 cm) wire screen (no. 4 mesh) which was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen was determined. Inability to climb to the top within one minute was defined as "neurological impairment". This procedure is described in *Pharmacol. Biochem. Behav.* 6, 351–353 (1977) and is incorporated herein by reference with the same force and effect as if fully set forth herein.

The dose effect behavior of the compounds was evaluated using the above-described procedures by the administration of varying dose levels, treating normally eight mice at each dose. Table I includes an evaluation of the Median Effective Dose (ED50) and the Median Toxic Dose (TD50) of representative compounds. Mice were tested with varying doses of the anticonvulsant to define the limits of complete protection (or toxicity) and no protection (or no toxicity), as well as three points in between these limits. The Median Effective Dose (ED50) was defined as the dose which produced the desired endpoint in 50% of the animals. The Median Toxicity Dose (TD50) was the dose which elicited evidence of minimal neurological toxicity in 50% of the animals.

More specifically, data tabulated in Table 1 were generated as follows:

The compound was given in various dose levels (i.e., 10, 30, 100, 300 mg) and subsequently compared with phenytoin, phenobarbital, mephenytoin and phenacemide (See Table I). N-Acetyl-D,L-alanine-N'-benzylamide was tested at 600 mg/mL as well. Seizures were then artifically induced by either electroschock or pentylenetetrazole. Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50 mA intensity (5–7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 sec via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. The Subcutaneous Pentylenetetrazole (Metrazol™) Seizure Threshold Test (sc Met) entailed the administration of 85 mg/kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline. This amount of pentylenetetrazole was expected to produce seizures in greater than 95% of mice. The animal was observed for 30 minutes. Protection was defined as a failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 sec duration). The results of these tests are tabulated in Table I.

TABLE I

Comparative Median Effective Dosage

| Compound | Tox TD50 mg/kg | MES ED50 mg/kg | sc Met ED50 mg/kg |
|---|---|---|---|
| N-acetyl-D,L-alanine-N'-benzylamide | 454 (417–501)* | 77 (67–89)* | ≠ |
| N-acetyl-D-alanine-N'-benzylamide | 214 (148–262)* | 55 (50–60)* | 55 (43–67)* |
| N-acetyl-L-alanine-N'-benzylamide | 841 (691–594)* | 548 (463–741)* | ≠ |
| N-acetyl-D,L-phenylglycine-N'-benzylamide | >>40 | 32.1 | ≠ |
| N-acetyl-D-phenylglycine-N'-benzylamide | >>80 | 26.4 | ≠ |
| N-acetyl-L-phenylglycine-N'-benzyl- | 100–300 | >300 | ≠ |

TABLE I-continued

Comparative Median Effective Dosage

| Compound | Tox TD50 mg/kg | MES ED50 mg/kg | sc Met ED50 mg/kg |
|---|---|---|---|
| amide | | | |
| D,L-α-acetamido-N-benzyl-3-thiophene-acetamide | >100 | 87.80 | ≠ |
| D,L-α-acetamido-N-benzyl-2-thiophene-acetamide | 30–100 | 44.80 | ≠ |
| D,L-α-acetamido-N-benzyl-2-furan-acetamide | 40 | 10.33 | ≠ |
| D,L-α-acetamido-N-benzyl-2-pyrrole-acetamide | <100 | 16.10 | ≠ |
| D,L-2-acetamido-N-benzyl-2-ethoxy-acetamide | >112 | 62.01 | ≠ |
| D,L-2-acetamido-N-benzyl-2-methoxy-acetamide | <300 | 98.30 | ≠ |
| (D,L)-α-Acetamido-N-benzyl-2-(5-methylfuran) acetamide | 75.4[xx] | 19.2 (16.4–23.8)* | ≠ |
| (D,L)-α-Acetamido-N-benzyl-2-benzofuran-acetamide | >100<300[xx] | >100<300 | ≠ |
| (D,L)-α-Acetamido-N-benzyl-2-benzo[b]-thiopheneacetamide | >100<300[xx] | >100<300 | ≠ |
| (D,L)-α-Acetamido-N-benzyl-2-(5-methylpyrrole) acetamide | x | 36.5 (30.6–57.1)* | ≠ |
| (D,L)-α-Acetamido-N-(2-fluorobenzyl)-2-furan-acetamide | x | 40.0 | ≠ |
| (D,L)-α-Acetamido-N-(3-fluorobenzyl)-2-furan-acetamide | 135.6 (114.9–161.8)[xx] | 13.3 (11.5–15.3)* | ≠ |

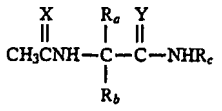
| | Tox TD 50 mg/kg | MES ED 50 mg/kg | scMet ED 50 mg/kg |
|---|---|---|---|
| 2-acetamido-N-benzyl-2-aminoacetamide | ≠ | 65.1 (56.2–75.3) | ≠ |
| 2-acetamido-N-benzyl-2-(1-Pyrrolyl) acetamide | ≠ | 80.2 | ≠ |
| 2-acetamido-N-benzyl-2-(1-imidazo γ1) acetamide | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide | ≠ | 45.3 | ≠ |
| 2-acetamido-N-benzyl-2-(4-morpholine)acetamide | ≠ | >30, <100 | ≠ |
| 2-acetamido-N-benzyl-2-(N,N,N-trimethylammonium) acetamide tetrafluoroborate | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(N-anilino)acetamide | ≠ | >300 | ≠ |
| 2-acetamido-N-benzyl-2-(N-(3-pyrazolylamino)) acetamide | ≠ | ~100 | ≠ |
| 2,2-diacetamido-N-benzyl-acetamide | ≠ | >100, <300 | ≠ |
| 2-acetamido-N-benzyl-2-trifluoroacetamidoacetamide | ≠ | >300 | ≠ |
| 2-acetamido-N-benzyl-2-(N-hydroxyamino)acetamide | ≠ | ~100 | ≠ |
| 2-acetamido-N-benzyl-2-(N-methoxyamino)acetamide | 46.0[xx] | 6.2 | ≠ |
| 2-acetamido-N-benzyl-2-(N,(N-methylhydroxyamino)) acetamide | (38.0 . 56.0) ≠ | (5.4–7.2) ~30 | ≠ |
| 2-acetamido-N-benzyl-2-(N-(N,O-dimethylhydroxy-amino)acetamide | 50.5[xx] (40.4–59.9) | 6.7 (5.7–7.7) | ≠ |
| 2-acetamido-N-benzyl-2-(N-isoxazolidino)acetamide | ≠ | 31.4 (26.7–37.8) | ≠ |
| 2-acetamido-N-benzyl-2-($N^2$-phenylhydrazino) acetamide | ≠ | ~100 | ≠ |
| 2-acetamido-N-benzyl-2-($N^2$-benzyloxycarbonyl-hydrazino)acetamide | ≠ | 55.6 (49.3–63.9) | ≠ |
| 2-acetamido-N-benzyl-2-hydroxyacetamide | ≠ | 80.1 (70.6–91.0) | ≠ |
| 2-acetamido-N-benzyl-2-(1-Pyrazolyl) acetamide | ≠ | 16.5 (14.1–22.5) | ≠ |
| 2-acetamido-N-benzyl-2-phenoxyacetamide | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(methylmercapto)acetamide | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide | ≠ | >30, <100 | ≠ |
| 2-acetamido-N-benzyl-2-(S-thiophenoxy)acetamide | ≠ | >300 | ≠ |
| 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomer A) | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomers A + B) | ≠ | >100 | ≠ |
| 2-acetamido-N-benzyl-2-(ethylsulfonyl)acetamide | ≠ | >100 | ≠ |
| (D,L)-α-Acetamido-N-(4-fluorobenzyl)-2-furan-acetamide | 144.4 (122.5–170.9)[xx] | 12.7 (10.4–15.1)* | ≠ |
| (D,L)-α-Acetamido-N-(2,5-difluorobenzyl)-2-furan-acetamide | x | 23.8 (20.2–28.4)* | ≠ |
| (D,L)-α-Acetamido-N-(2,6-difluorobenzyl)-2-furan-acetamide | x | >25>100 | ≠ |
| (D)-(−)-α-Acetamido-N-benzyl-2-furanacetamide | 23.8[xx] | 3.3 (2.8–3.9)* | ≠ |
| (L)-(+)-α-Acetamido-N-benzyl-2-furanacetamide | >300 | >100<300 | ≠ |
| (D,L)-2-Acetamido-4-pentenoic acid-N-benzylamide | x | 33.6 | ≠ |
| 2-acetamido-N-benzyl-2-(2-Pyridyl) acetamide | ≠ | 8.5 | ≠ |
| (D,L)-2-Acetamido-N-benzyl-2-(methylamino)acetamide | 95.0 | 44.5 (37.0–52.4)* | ≠ |
| (D,L)-2-Acetamido-N-benzyl-2-(ethylamino)acetamide | x | 42.4 (37.2–47.8)* | ≠ |
| (D,L)-2-Acetamido-N-benzyl-3-indoleacetamide | x | xxx | ≠ |
| phenytion | 66 | 10 | not effective |
| phenobarbital | 69 | 22 | 13 |
| mephenytion | 154 | 61 | 31 |
| phenacemide | 421 (337–549)* | 87 (74–100)* | 116 (71–150)* |

*95% confidence intervals.
≠ or x The TD50 for this substrate was not computed.
[xx]The TD50 value was determined using the horizontal screen test.
xxx No activity was noted at ≦300 mg/kg

Other results from the pharmacological protocols are summarized in Tables II, III and IV.

TABLE II

Selected Physical and Pharmacological Data in Mice for α-Acetamido-N-benzyl-2-furanacetamide (2)-Derivatives.[a]



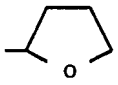
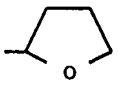
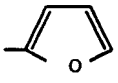
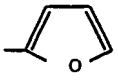
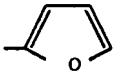
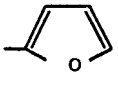
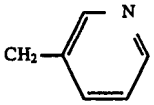
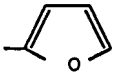
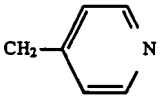
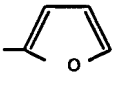
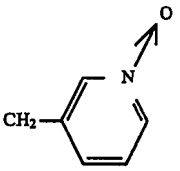
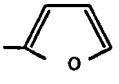
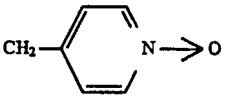
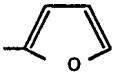
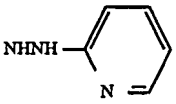
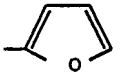
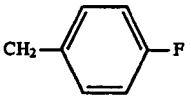
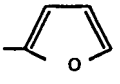
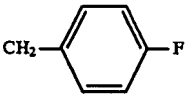
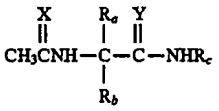
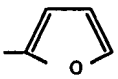
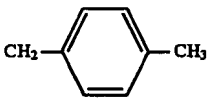
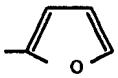
| CMP # | Ra | Rb | Rc | X | Y | mp[b] | MES[c] $ED_{50}$ mg/kg | Tox[d] $TD_{50}$ mg/kg | PI[e] |
|---|---|---|---|---|---|---|---|---|---|
| 3a |  | H | $CH_2CH_6H_5$ | O | O | 159–161 | 51.7 (44.4–59.9) | f | — |
| 3b |  | H | $CH_2C_6H_5$ | O | O | 130–132 | 89.8 (78.4–103.4) | f | — |
| 4 |  | $CH_3$ | $CH_2C_6H_5$ | O | O | —[h] | >300 | f | — |
| 5 |  | H | $CH_2C_6H_5$ | S | O | 78–80 | 18.4 (15.9–22.0) | f | — |
| 6 |  | H | $CH_2C_6H_5$ | S | S | 99–101 | >100 | f | — |
| 7 |  | H |  | O | O | 172–174 | ~30 | f | — |
| 8 |  | H |  | O | O | 168–170 | >100 | f | — |
| 9 |  | H |  | O | O | 159–161 | ~30 | f | — |
| 10 |  | H |  | O | O | 210–212 | >100 | f | — |
| 11 |  | H |  | O | O | 226–228 | >100 | f | — |
| 12 |  | H |  | O | O | 188–190 | 12.7 (10.4–15.1) | 144 (123–171) | 11.3 |
| (R)-12 |  | H |  | O | O | 206–207 | 3.5 (2.9–4.4) | 14.4 (7.3–28.9) | 4.1 |

TABLE II-continued

Selected Physical and Pharmacological Data in Mice for α-Acetamido-N-benzyl-2-furanacetamide (2)-Derivatives.[a]

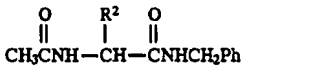


| CMP # | Ra | Rb | Rc | X | Y | mp[b] | MES[c] $ED_{50}$ mg/kg | Tox[d] $TD_{50}$ mg/kg | PI[e] |
|---|---|---|---|---|---|---|---|---|---|
| (R)-13 |  | H |  | O | O | 210–212 | <10 | f | — |
| (R)-14 |  | H |  | O | O | 193–195 | >10, <30 | f | — |
| phenytoin | | | | | | | 9.5 (8.1–10.4) | 65.5[i] (52.5–72.1) | 6.9 |
| phenobarbital | | | | | | | 21.8 (15.0–22.5) | 69.0[i] (62.8–72.9) | 3.2 |
| valproate | | | | | | | 272 (247–338) | 426[i] (369–450) | 1.6 |

[a]The compounds were administered intraperitoneally. $ED_{50}$ and $TD_{50}$ values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets.
[b]Melting points (°C.) are uncorrected.
[c]MES = maximal electroshock seizure test. Compound was suspended in 30% PEG.
[d]Tox = neurologic toxicity determined from horizontal screen unless otherwise noted.
[e]PI = protective index ($TD_{50}ED_{50}$).
f Not determined.
[i]Thick oil.

TABLE III

Selected Physical and Pharmacological Data in Mice for N-Substituted α,α-Diamino Acid Derivatives.[a]



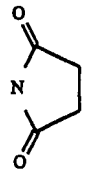
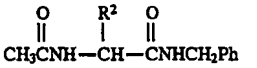
| no | $R^2$ | mp[b] | MES[c] $ED_{50}$ | tox[d] $TD_{50}$ |
|---|---|---|---|---|
| 2e | $NHC(O)CH_3$ | 202–204 | >30, <100 | e |
| 2f | NHC(O)OPh | 201–203 | >100 | e |
| 2g | $NHC(O)NHCH_3$ | 229–230 | >100 | e |
| 2h | NHC(O)NHPh | 242–244 | >100 | e |
| 2i | $NHC(O)NHS(O_2)Ph$ | 188–191 | >100 | e |
| 2j | $NHC(S)NHCH_3$ | 162–163 | >100 | e |
| 2k | NHC(S)NHPh | 196–197 | >100 | e |
| 2l | NHC(O)Ph(2'-$CO_2H$) | 186–188 | >100 | e |
| 2m |  | 181–183 | >100 | e |
| 2n | $NHC(O)CH_2NHC(O)OCH_2Ph$ | 177–179 | >10, <30 | e |
| 2o | $NHCH_2C(O)OCH_2CH_3$ | 125–127 | >100 | e |
| 2p | $NHCH_2C(O)OCH_2Ph$ | 133–135 | 72 | 74 |
| 2q | $^+NH_2CH_2CO_2^-$ | 124–126 | | |

TABLE III-continued

Selected Physical and Pharmacological Data in Mice for N-Substituted α,α-Diamino Acid Derivatives.[a]

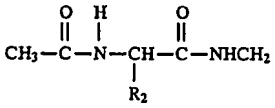


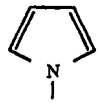
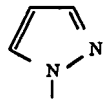
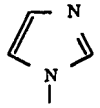
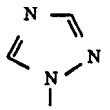
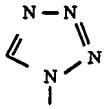
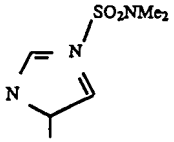
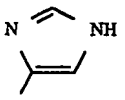
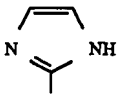
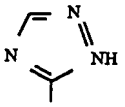
| no | $R^2$ | mp[b] | MES[c] $ED_{50}$ | tox[d] $TD_{50}$ |
|---|---|---|---|---|
| phenytoin | | | 95 (8.1–10.4) | 65.5[f] (52.5–72.1) |
| pheno-barbital | | | 21.8 (15.0–22.5) | 69.0[f] (62.8–72.9) |
| valproate | | | 272 (247–338) | 426[f] (369–450) |

[a]The compounds were administered intraperitoneally. $ED_{50}$ and $TD_{50}$ values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets.
[b]Melting points (°C.) are uncorrected.
[c]MES = maximal electroshock seizure test. Compound was suspended in 30% PEG unless otherwise noted.
[d]Tox = neurologic toxicity determined from horizontal screen unless otherwise noted.
e Not determined.
[f]Neurologic toxicity determined using the rotorod test.

TABLE IV

Pharmacological Data in Mice for α-Acetamido-N-Benzyl-2-Heterocyclic Derivatives



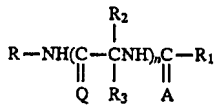
| $R_2$ | MES[a] $ED_{50}$ | tox[b] $TD_{50}$ |
|---|---|---|
|  | 80.2 | — |
|  | 16.5 | 66.9 (55.6–81.1) |
|  | >100 | — |
|  | >30, <100 | — |
|  | >300 | |
|  | >100 | — |
|  | >100 | >100 |
|  | >100 | — |
|  | >100 | — |

[a]MES = maximal electroshock seizure test. Compound was suspended in 30% PEG.
[b]TOX = neurologic toxicity determined from horizontal screen unless otherwise noted.

Thus, while the invention has been described with reference to certain preferred embodiments, those skilled in the art will realize that changes and modifications may be made thereto without departing from the full and intended scope of the appended claims.

What is claimed is:

1. A compound of the formula

 (I)

or the N-oxide thereof or pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl, cycloalkyl, lower cycloalkyl, lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

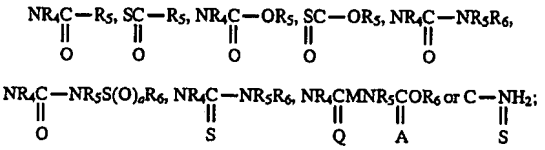
$R_1$ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic lower cycloalkyl, lower cylcoalkyl, lower alkyl, and $R_1$ is unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

$R_1$ and $R_3$ are independently hydrogen, lower alkyl lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, $SO_3$[31] or Z—Y wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, $S(O)_a$, $NR_4$, mercaptoalkyl, alkylthio; or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic or heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower alkyl and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group provided that Z is a chemical bond only when Y is halo; or

ZY taken together is $NR_4NR_5R_7$, $NR_4OR_5$, $ONR_4R_7$, $SNR_4R_7$, $NR_4SR_7$, $SPR_4R_5$,



$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

$R_7$ is $R_6$, $COOR_8$ or $COR_8$;

$R_8$ is hydrogen or lower alkyl or aryl lower alkyl;

n is 1–4 and

a is 1–3

M is a lower alkylene chain, and A and Q are independently O or S with the provisio that at least one of A or Q is S.

2. The compound, according to claim 1 wherein A is S.

3. The compound according to claim 1 wherein A and Q are S.

4. The compound according to claim 1 wherein one of $R_2$ and $R_3$ is H.

5. The compound according to claim 4 wherein one of $R_2$ and $R_3$ is H and the other is heterocyclic.

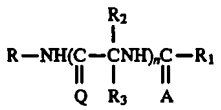
6. The compound according to claim 5 wherein heterocyclic is furyl, pyrrolyl, pyrazoyl, epoxy, oxazolyl, imidazolyl, tetraxolyl, triazolyl, or oxadiaxoyl.

7. The compound according to claim 6 wherein heterocyclic is furyl, pyrrolyl, pyrozolyl, or pyridyl.

8. The compound according to claim 1 wherein one of $R_2$ and $R_3$ is H and the other is Z—Y.

9. The compound according to claim 8 wherein Z—Y is N,O-dimethylhydroxyamino, N-methylhydroxyamino N-methyoxyamino, ethylamino or methylamino or hydrazino.

10. A compound of the formula



(I)

or the N-Oxide thereof or pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl, cycloalkyl, lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

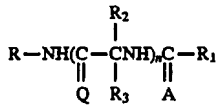
$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

one of $R_2$ and $R_3$ is hydrogen, and the other is $SO_3$—,

A and O are independently O or S and n is 1–4.

11. The compound according to claim 10 wherein Q and A are both O.

12. A compound of formula



(I)

or the N-Oxide thereof or pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl, cycloalkyl, lower cycloalkyl, lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

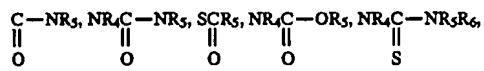
$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

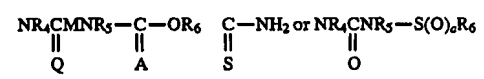
$R_2$ and $R_3$ are independently hydrogen, alkyl, or Z—Y wherein $R_2$ and $R_3$ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is $S(O)_a$, mercaptoalkyl, or alkylthio

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic or heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower alkyl and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group provided that when Y is halo, Z is a chemical bond; or

ZY taken together is $NR_4$





$R_4$, $R_5$ and $R_6$ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein $R_4$, $R_5$ and $R_6$ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group;

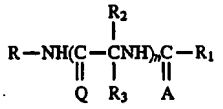
n is 1–4 and

a is 1–3

M is lower alkylene, and A and Q are independently O or S with the provisio that at least one of $R_2$ and $R_3$ is Z—Y.

13. The compound of claim 12 wherein A and Q are both oxygen.

14. A compound of the formula



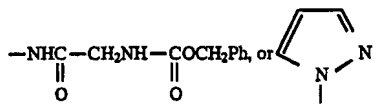
(I)

or the N-Oxide thereof or pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic or heterocyclic lower alkyl, cycloalkyl, lower cycloalkyl, lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

$R_1$ and $R_3$ are independently hydrogen, amino, pyrrolyl, N, N-dimethylamino, morpholinyl, pyrazinyl, —NH $OCH_3$, methylhydroxyamino, (N,O—) dimethylhydroxyamino



or epoxy, and n is 1–4, provided that at least one of $R_2$ and $R_3$ is other than hydrogen.

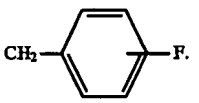
15. The compound according to claim 14 wherein Q and A are both O.

16. The compound according to any one of claims 1–15 wherein n is 1.

17. The compound according to any one of claims 1–15wherein R is lower arylalkyl which is unsubstituted or substituted with an electron donating group or electron withdrawing group.

18. The compound according to claim 17 wherein R is benzyl which is unsubstituted or substituted with an electron withdrawing group or electron donating group.

19. The compound according to claim 18 wherein R is unsubstituted benzyl or



20. The compound according to any of claims 1–15 wherein $R_1$ is lower alkyl.

21. The compound according to claim 20 wherein $R_1$ is methyl.

22. A compound selected from the group consisting of ethyl 2-acetamido-2-aminoacetate, ethyl 2-acetamido-2-(methylamino)acetate, ethyl 2-acetamido-2-(N,N-dimethylamino)acetate, ethyl 2-acetamido-2-(4-

morpholine)acetate, ethyl 2-acetamido-2-(N-anilino)acetate, ethyl 2-acetamido-2-(N-(3-pyrazolylamino))acetate, ethyl 2-acetamido-2-(N-hydroxyamino)acetate, ethyl 2-acetamido-2-(N-(N-methylhydroxyamino))acetate, ethyl 2-acetamido-2-(N-(N,O-dimethylhydroxyamino))acetate, 2-acetamido-N-benzyl-2-aminoacetamide, 2-acetamido-N-benzyl-2-(methylamino)acetamide, 2-acetamido-N-benzyl-2-(ethylamino)acetamide, 2-acetamido-N-benzyl-2-(N-anilino)acetamide, 2-acetamido-N-benzyl-2(N-(3-pyrazolylamino))acetamide, 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide, 2-acetamido-N-benzyl-2-(N-hydroxyamino)acetamide, 2-acetamido-N-benzyl-2-(N-hydroxyamino)acetamide, 2-acetamido-N-benzyl-2-($N^2$-phenylhydrazino)acetamide, 2-acetamido-N-benzyl-2-($N^2$-benzyloxycarbonylhydrazino)acetamide, 2-acetamido-N-benzyl-2-phenoxyacetamide, 2-acetamido-N-benzyl-2-(methylmercapto)acetamide, 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide, 2-acetamido-N-benzyl-2-(N-methoxyamino)acetamide, 2-acetamido-N-benzyl-2-(N-(N-methylhydroxyamino))acetamide, 2-acetamido-N-benzyl-2-(N-(N,O-dimethylhydroxyamino))acetamide, 2-acetamido-N-benzyl-2-(N-isoxazolidino)acetamide, 2-acetamido-N-benzyl-2-hydroxyacetamide, 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide, 2,2-diacetamido-N-benzylacetamide, 2-acetamido-N-benzyl-2-trifluoracetamidoacetamide, 2-acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate, 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide, 2-acetamido-N-benzyl-2-(S-ethylmercapto) acetamide-S-oxide, 2-acetamido-N-benzyl-2-(ethanesulfonyl)acetamide, 2-acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate, 2-acetamido-N-benzyl-2-(1-pyrrole)acetamide, 2-acetamido-N-benzyl-2-(1-imidazole)acetamide, 2-acetamido-N-benzyl-2-(1-pyrazole)acetamide, 2-acetamido-N-benzyl-2(1-(1,2,4-triazole))acetamide, 2-acetamido-N-benzyl-2(1-tetrazole))acetamide, α-acetamido-N-benzyl-2-pyridylacetamide, α-acetamido-N-benzyl-2-pyridyl acetamide N-oxide, α-acetamido-N-benzyl-2-(S-thiophenoxy)-acetamide, α-acetamido-N-benzyl-2-(tetrahydrofuran)acetamide, methyl α-acetamido-2-methyl-2-furanacetate, α-acetamido-2-methyl-2-furanacetic acid, α-acetamido-N-benzyl-2-methyl-2-furanacetamide, α-thioacetamido-N-benzyl-2-furanacetamide, α-thioacetamido-N-benzyl-2-furanthioacetamide, α-acetamido-N-(3-pyridinylmethyl)-2-furanacetamide, α-acetamido-N-(4-pyridinylmethyl)-2-furanacetamide, α-acetamido-N-(1-oxo-3-pyridinylmethyl) -2-furanacetamide, α-acetamido-N-(1-oxo-4-pyridinylmethyl)-2-furanacetamide, R(−)α-acetamido-N-(4-fluorobenzyl)-2-furanacetamide, R(−)α-acetamido-N-(4-trifluoromethylbenzyl)-2-furanacetamide, methyl [acetamido(benzylcarbamoyl)methyl]carbomate, phenyl [acetamido(benzylcarbamoyl)methyl]carbomate, 1-[acetamido(benzylcarbamoyl)methyl]-3-methylurea), 1-[acetamido(benzylcarbamoyl)methyl]-3-phenylurea), 1-[acetamido(benzylcarbamoyl)methyl]-3-benzenesulfonylurea), 1-[acetamido(benzylcarbamoyl) methyl]-3-methylthiourea), 1-[acetamido(benzylcarbamoyl) methyl]-3-phenylthiourea), N-[acetamido (benzylcarbamoyl)methyl]phthalamic acid), 2-acetamido-N-benzyl-2-(N-succinimidyl)acetamide), benzyl N-[acetamido(benzylcarbamoyl)methyl]malonamate, ethyl N-[acetamido(benzylcarbamoyl)methyl]glycinate, benzyl N-[acetamido(benzylcarbamoyl)methyl]glycinate, N-[acetamido(benzylcarbomoyl)methyl]glycine, 2-acetamide-N-benzyl-2-(1-pyrrole)acetamide, 2-acetamido-N-benzyl-2-(1-pyrazole)acetamide, 2-acetamido-N-benzyl-2-(1-imidazole)acetamide. 2-acetamido-N-benzyl-2-(1-(1,2,4-triazole))acetamide, 2-acetamido-N-benzyl-2-(1-tetrazole))acetamide, α-acetamido-N-benzyl-1-(dimethylsulfamoyl)imidazole-4-acetamide, α-acetamido-N-benzyl-4-imidazole acetamide, α-acetamido-N-benzyl-2-imidazole acetamide, α-acetamido-N-benzyl-5-(tetrazole)acetamide, α-acetamido-N-benzyl-3-(1,2,4-triazole)acetamide. α-acetamido-N-benzyl-2-(carboxamide oxime)acetamide, α-acetamido-N-benzyl-2-(carboxamide oxime-(O-acetate))-acetamide, α-acetamido-N-benzyl-3-(1,2,4-oxadiazole) acetamide, α-acetamido-N-benzyl-2-(thioamide) acetamide), 2-acetamido-N-benzyl-2-vinylacetamide, 2-acetamido-N-benzyl-2-epoxyacetamide, potassium 2-acetamido-N-benzylacetamide-2-sulfonate, 2-acetamido-4-pentenic acid-N-benzylamide, α-acetamido-N-benzyl-2-(2-oxazole)-acetamide, and α-acetamido-N-benzyl-2-(2-thiazole)-acetamide.

**23.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claims **1–15** and **22** and a pharmaceutical carrier therefor.

**24.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from claim **16** and a pharmaceutical carrier therefor.

**25.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from claim **17** and a pharmaceutical carrier therefor.

**26.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from claim **18** and a pharmaceutical carrier therefor.

**27.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound of claim **19** and a pharmaceutical carrier therefor.

**28.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound of claim **20** and a pharmaceutical carrier therefor.

**29.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound of claim **21** and a pharmaceutical carrier therefor.

**30.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound according to any one of claims **1–15** and **22**.

**31.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **16**.

**32.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **17**.

**33.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **18**.

**34.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **19**.

**35.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **20**.

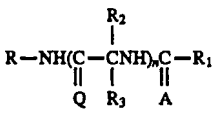
**36.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of claim **21**.

**37.** The compound according to any one of claims **1**, **10**, **12** or **14** wherein n is 1 and R is lower alkyl which is unsubstituted or substituted with an electron donating group or electron withdrawing group.

**38.** The compound according to any one of claims **1**, **10**, **12** or **14** wherein n is 1; $R_1$ is methyl and R is lower arylalkyl

which is unsubstituted or substituted with an electron withdrawing group or electron donating group.

**39.** A compound of the formula



(I)

or the pharmaceutically acceptable salts thereof wherein

R is aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl or lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;

$R_1$ is hydrogen or lower alkyl and $R_1$ is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;

A and Q are both O;

one of $R_2$ and $R_3$ is hydrogen and the other is lower alkyl which is substituted with an electron donating group or a electron withdrawing group and n is 1–4.

**40.** The compound according to claim **39** wherein one of $R_2$ and $R_3$ is hydrogen and the other is lower alkyl substituted with an electron donating group.

**41.** The compound according to claim **40** wherein one of $R_2$ and $R_3$ is alkyl substituted with an electron donating group wherein alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl or hexyl.

**42.** The compound according to claim **41** wherein one of $R_2$ and $R_3$ is methyl substituted with an electron donating group.

**43.** The compound according to claim **42** wherein the electron donating group is lower alkoxy.

**44.** The compound according to claim **43** wherein lower alkoxy is methoxy.

**45.** The compound according to any one of claims **39–44** wherein n is 1.

**46.** An anti-convulsant composition comprising an anti-convulsant effective amount of a compound from any one of claim **37–42** and a pharmaceutical carrier therefor.

**47.** A method of treating CNS disorders in an animal comprising administering to said animal an anti-convulsant effective amount of a compound of any one of claims **39–44**.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 5,654,301
DATED : August 5, 1997
INVENTOR(S) : Harold Kohn, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 34,
Line 59: "Ch $_3$ H)" should read -- $C_3$ H) --
Line 59: "8.62 Hz" should read -- 8.62 (d,J=7.7 --
Line 60: "H," should read -- Hz, --

Column 35,
Line 15: "form" should read -- formed --
Line 35: "8.89" should read -- 8.99 --

Column 37,
Line 53: "α" should read -- 2 --
Line 60: "or" should read -- of --

Column 38,
Line 65: "$13_c$" should read -- 13 $_C$ --

Column 40,
Line 25: "2.33" should read -- 2.23 --
Line 25: "425" should read -- 4.25 --
Line 67: "($M^{30}$=1)" should read -- ($M^+$= 1) --

Column 41,
Line 25: "2-hydroxyamino" should read -- 2-(N-hydroxyamino) --

Column 42,
Line 55: "($M^+$ + 100)" should read -- ($M^+$ + 1,100) --

Column 19,
Line 30: "intraperitoncally" should read -- intraperitoneally --

Column 27,
Line 45: "16 ° " should read -- 169 ° --

Column 28,
Line 56: "7.1.7" should read -- 7.17 --

Column 30,
Line 37: "63" should read -- 6.3 --
Line 64: "785" should read -- 735 --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 5,654.301
DATED : August 5, 1997
INVENTOR(S) : Harold Kohn, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 31,
Line 21: "cbloroform" should read -- chloroform --
Line 49: "2.78" should read -- 2.75 --

Column 33,
Line 16: "(D,L" should read -- (D,L) --
Line 38: "94:4" should read -- 96:4 --
Lines 41 & 42: "80" should read -- 8.0 --
Line 48: "$C_{3'}$ "should read -- $C_{6'}$ --

Column 34,
Line 15: "130" should read --139 --
Line 41: "M + 1" should read -- $M^+$ + 1 --

Column 43,
Lines 21 & 49: "acetamido" should read -- acetamide --
Line 59: "1.84'" should read -- 1.84 --

Column 44,
Line 46, "n" should read -- a --
Line 46: "ethoxyacetamido" should read -- ethoxyacetamide --
Line 65: "acetamido" should read -- acetamide --

Column 45,
Line 18: after "spectrum" insert -- (FD) --
Line 39: "7.5" should read -- 7.52 --
Line 56: "73.3" should read -- 7.33 --

Column 46,
Line 25: "$CH_3Cl_2$," should read -- $CH_2Cl_2$ --

Column 49,
Lines 57-58: "O-methylhydroxyamino" should read -- O-dimethylhydroxyamino --

Column 50,
Line 40: "149" should read -- 14.9 --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 5,654.301
DATED : August 5, 1997
INVENTOR(S) : Harold Kohn, et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 51,
Line 24: "accetamido" should read -- acetamide --
Line 38: "Dicacetamido" should read -- Diacetamide --
Line 46: "and-was" should read -- and was --

Column 52,
Line 16: "166.3.9" should read -- 166.39 --

Column 54,
Line 16: "Time" should read -- The --

Column 55,
Line 7: "H" should read -- It --

Column 56,
Line 55: "$C_1$ " should read -- $C_{12}$ --
Line 66: "while" should read -- white --
Line 66: "alter" should read -- after --

Column 58,
Line 30: "dr" should read -- dt --

Column 59,
Line 62: after "1.89" insert -- (s, --
Line 63: Delete -- (s, --

Column 60,
Line 4: "1" should read -- 91 --

Column 61,
Line 30: "($C_2$), H" should read -- $CH_2$ ), --

Column 63,
Line 38: "add" should read -- acid --

Column 65,
Line 10: "8.62" should read -- 8.61 --
Line 21: "arthydride" should read -- anhydride --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 5,654.301
DATED : August 5, 1997
INVENTOR(S) : Harold Kohn, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 66,
Line 34: "600" should read -- 670 --

Column 67,
Line 22: "63.72" should read -- 63.22 --
Line 63: "170.30" should read -- 170.03 --
Line 66: "$N_{402}$" should read -- $N_4$ $O_2$ S --

Column 68,
Line 9: "while" should read -- white --
Line 67, "1.80" should read -- 181 --

Column 69,
Line 8: "176.5" should read -- 176.33 --
Lines 45-46: "Found: C,60.90: C, 61.16; H, 587; N, 1358.H, 5.77; N, 13.35." should read -- C, 61.16;H, 5.87; N, 13.58. Found: C, 60.90; H,5.77;N, 13.35. --
Line 57: "29o" should read -- 2o --

Column 70,
Line 41: "2g" should read 2q --

Column 76,
Line 3: "BF3" should read -- $BF_3$ --
Line 37, "NHH" should read -- NHH' --

Column 81,
Line 47: "imidazo" should read -- imidazoyl --

Column 82,
Line 6: "38.0 . 56.0" should read -- 38.0-56.0 --

Column 83,
Line 15: "$CH_2$ $CH_6$ $H_5$" should read -- $CH_2C_6$ $H_5$ --

Column 84,
Line 63: "206" should read -- 205 --

Column 86,
Line 47: "95" should read -- 9.5 --

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 5,654.301
DATED : August 5, 1997
INVENTOR(S) : Harold Kohn, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 88, claim 1:
Line 24, "$SO_3^{31}$" should read -- $SO_3$ --

Column 89, claim 10:
Line 26, "O" should read -- A and Q --

Column 90, claim 14:
Line 28, "$R_1$" should read -- $R_2$ --

Column 90, claim 17:
Line 46, "1-15wherein" should read -- 1-16 wherein --

Column 90, claim 20:
Line 60, "1-15" should read -- 1-19 --

Signed and Sealed this

Twenty-seventh Day of November, 2001

*Attest:*

Nicholas P. Godici

*Attesting Officer*

NICHOLAS P. GODICI
*Acting Director of the United States Patent and Trademark Office*

# Exhibit E

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MASTER DATA CENTER, INC.
29100 NORTHWESTERN HIGHWAY
SUITE 300
SOUTHFIELD MI 48034-1095

# MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| **5,654,301** | **$850.00** | **$0.00** | **02/02/01** | **08/003,208** | **08/05/97** | **01/12/93** | **04** | **NO** | **5352ZYXI-IIW** |

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# MAINTENANCE FEE STATEMENT

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

| PATENT NUMBER | FEE AMT | SUR CHARGE | PYMT DATE | U.S. APPLICATION NUMBER | PATENT ISSUE DATE | APPL. FILING DATE | PAYMENT YEAR | SMALL ENTITY? | ATTY DKT NUMBER |
|---|---|---|---|---|---|---|---|---|---|
| **5,654,301** | **$2,150.00** | **$0.00** | **12/03/04** | **08/003,208** | **08/05/97** | **01/12/93** | **08** | **NO** | **5352ZYXI-IIW** |

# Exhibit F

# Exhibit F

A brief description of significant activities undertaken by the sponsor, Schwarz Biosciences, Inc. ("Schwarz") (or its predecessor in interest), during the regulatory review period for VIMPAT® (lacosamide) injection, together with applicable dates, follows below.

## 1. Overview

Between November 14, 2003 and September 28, 2007, Schwarz conducted two clinical studies of VIMPAT® injection to identify the appropriate infusion duration(s) for VIMPAT® as short-term replacement for oral VIMPAT® and to provide data to support the safety of that infusion duration. Schwarz also conducted at least four pharmacokinetic and pharmacodynamic studies.

Between September 28, 2007 and October 28, 2008, Schwarz responded to numerous requests for information from FDA. The dates of those responses are summarized in Section 4.

## 2. Key Regulatory Dates

| | |
|---|---|
| October 15, 2003 | IND 68,407 submitted to FDA |
| November 14, 2003 | FDA notification (via telephone) that IND 68,407 is in effect |
| December 24, 2003 | FDA confirmation (via letter) that IND 68,407 is in effect[1] |
| December 9, 2004 | End-of-Phase II Meeting with FDA |
| July 19, 2006 | Pre-NDA Meeting with FDA |
| September 6, 2006 | Meeting with FDA regarding abuse liability |
| September 28, 2007 | NDA 22-254 submitted to FDA |
| October 22, 2007 | FDA letter acknowledging receipt of NDA |
| December 10, 2007 | FDA letter accepting NDA for filing |
| July 31, 2008 | FDA letter extending NDA review date until October 28, 2008 |
| October 28, 2008 | FDA approval letter of NDA 22-254 |

[1] Applicant notes that IND 57,939 for VIMPAT® (lacosamide) tablet went into effect on May 19, 1999. Thus, certain dates relating to that IND may be relevant should the FDA determine that the present application is entitled to that date. Applicant will supplement this Exhibit upon request should information from IND 57,939 be determined by the FDA to be relevant.

## 3. Summary of Phase III Clinical Studies

| Start | Stop | Study |
|---|---|---|
| FSI 04 Mar 2004 | LSO 17 Aug 2004 | SP616 (multicenter, double-blind, double-dummy randomized study to investigate safety, tolerability, and pk of intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizures with or without secondary generalization) |
| FSI 03 Feb 2005 | LSO 10 May 2006 | SP757 (multicenter, open-label study to investigate the safety and tolerability of intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizures with or without secondary generalization) |

## 4. NDA Amendments

Following the initial submission of the NDA on September 28, 2007, Schwarz submitted additional information to FDA on the following dates:

November 26, 2007
December 13, 2007
January 23, 2008
February 13, 2008
February 22, 2008
March 20, 2008
April 3, 2008
April 9, 2008
April 14, 2008
April 18, 2008
April 30, 2008
May 9, 2008
May 27, 2008
June 11, 2008
July 11, 2008 (2)
July 17, 2008
July 30, 2008
August 1, 2008
August 14, 2008
August 27, 2008
September 4, 2008
September 23, 2008
October 15, 2008
October 21, 2008

## 5. Additional Information

A more detailed description of the activities undertaken by the NDA holder, including those otherwise listed above in this Exhibit, is set forth in the IND 68,407 Submissions and NDA 22-254 Submissions tables (each table being produced across multiple pages that are independently numbered) produced on the remainder of the pages of this Exhibit.

# IND 68,407 Submissions

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 15-Oct-03 | 0000 | | Initial IND | SP616 | Draft protocol | | |
| 15-Oct-03 | 0000 | | Initial IND | | Evaluation of the pharmacokinetic profile of SPM 927 | | |
| 15-Oct-03 | 0000 | | Initial IND | | Investigator brochure | | |
| 15-Oct-03 | 0000 | | Initial IND | SP658 | Randomized, open-label, single-dose, three-way crossover trial to compare the pharmacokinetics of SPM 927 when given a intravenous solution or as oral tablet in 24 healthy male subjects | | |
| 15-Oct-03 | 0000 | | Initial IND | SP643 | Randomized, open-label, two-way crossover trial to investigate the pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (cyp 2c19) | | |
| 15-Oct-03 | 0000 | | Initial IND | | Cross reference all preclinical and clinical reports from oral IND. | | |
| 03-Nov-03 | | | Response to FDA Request for Information | | Send Tom Broadbent, FDA, fax of certificate of analysis for DS, rationale for vials filled with 21.0mL, and 20 L beaker. | | |
| 04-Nov-03 | | | Response to FDA Request for Information | | Send Tom Broadbent, FDA, fax of detailed information on vial and beakers for IV formulation. | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 14-Nov-03 | | | FDA Phone Contact | | Ms. Griffis, FDA, calls with okay to proceed with IV trial SP616 and apology for comments on safety package being delayed. | | |
| 18-Nov-03 | 0001 | | Initial Safety Report | SP665 | | 2003-00393 | 10344 |
| 19-Nov-03 | 0002 | v1 p1 | Information Amendment: Clinical | SP600 | Open-label randomized, single dose, two-way cross-over study to evaluate the effect of food on the bioavailability of SPM 927 (harkoseride) in healthy male caucasian volunteers. | | |
| 19-Nov-03 | 0002 | v3 p1 | Information Amendment: Clinical | SP601 | Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of SPM 927 (harkoseride) on valproic acid (VPA) in 16 healthy male caucasian volunteers. | | |
| 02-Dec-03 | 0003 | | Follow-up Safety Report | SP667 | | 2002-00244 | 12803/80017 |
| 03-Dec-03 | 0004 | | Follow-up Safety Report | SP655 | | 2002-00095 | 10001/80037 |
| 05-Dec-03 | 0005 | | Initial Safety Report | SP667 | | 2003-00287 | 10404/80291 |
| 05-Dec-03 | 0006 | | Follow-up Safety Report | SP615 | | 2002-00044 | 10027/10027 |
| 08-Dec-03 | 0007 | | General Correspondence | | Schwarz sends correction letter to 5-dec-2003 serial no. 0006. Incorrect version of CIOMS report was attached. | | |
| 17-Dec-03 | 0008 | | Follow-up Safety Report | SP615 | | 2003-00248 | 10502 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 18-Dec-03 | 0009 | | Protocol Amendment: New Protocol | SP616 | New protocol | | |
| 19-Dec-03 | 0010 | | Initial Safety Report | SP615 | | 2003-00450 | 11488 |
| 23-Dec-03 | 0011 | | Follow-up Safety Report | SP667 | | 2003-00287 | 10404/80291 |
| 24-Dec-03 | | | FDA Correspondence | SP616 | FDA sends IND review letter with comments and recommendations regarding clinical, phamacokinetics, development plan and protocol SP616. | | |
| 30-Dec-03 | 0012 | | Initial Safety Report | SP615 | | 2003-00474 | 11503 |
| 09-Jan-04 | 0013 | | Information Amendment: CMC Data | | Revised CMC information including control of excipients, control of drug product and three month stability data for one batch of solution for injection. | | |
| 13-Feb-04 | 0014 | | Protocol Amendment: Change in Protocol | SP615 | Amendment 5 | | |
| 13-Feb-04 | 0014 | | Information Amendment: Clinical | SP619 | Open-label, randomized, single dose study to evaluate the absorption, metabolism, and excretion of [14C]-labeled SPM 927 (harkoseride) following oral and intravenous administration to 10 healthy male caucasian subjects | | |
| 13-Feb-04 | 0014 | | Protocol Amendment: Change in Protocol | SP616 | Amendment 1 | | |
| 13-Feb-04 | 0014 | | Response to FDA Request for Information | | Schwarz responds to FDA etter 24-dec-2003 comments and recommendations. | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 18-Feb-04 | 0015 | | Initial Safety Report | SP615 | | 2004-00049 | 11281 |
| 24-Feb-04 | 0016 | | Follow-up Safety Report | SP615 | | 2003-00474 | 11503 |
| 10-Mar-04 | 0017 | | General Correspondence | SP640 | Submit pain protocol SP640 to epilepsy INDs for information purposes only. | | |
| 18-Mar-04 | 0018 | | Protocol Amendment: New Investigator | SP616 | New investigators | | |
| 01-Apr-04 | 0019 | | Initial Safety Report | SP615 | | 2004-00129 | 11610 |
| 01-Apr-04 | 0019 | | Initial Safety Report | SP665 | | 2004-00135 | 10175 |
| 06-Apr-04 | 0020 | | Follow-up Safety Report | SP615 | | 2003-00248 | 10501 |
| 15-Apr-04 | 0021 | | Follow-up Safety Report | SP665 | | 2004-00135 | 10175 |
| 19-Apr-04 | 0022 | | Protocol Amendment: New Investigator | SP616 | New and Revised investigators | | |
| 03-May-04 | 0023 | | Initial Safety Report | SP615 | | 2004-00189 | 10185 |
| 12-May-04 | 0024 | | Follow-up Safety Report | SP615 | | 2004-00129 | 11610 |
| 19-May-04 | 0026 | | Initial Safety Report | SP615 | | 2004-00232 | 11478 |
| 20-May-04 | 0027 | | Protocol Amendment: New Investigator | SP616 | New investigator | | |
| 27-May-04 | 0028 | | Follow-up Safety Report | SP615 | | 2004-00049 | 11281 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 02-Jun-04 | | | 7-Day Safety Report | SP615 | Fax 7-day safety report to Ms. Griffis, FDA. | 2004-00274 | 11428 |
| 02-Jun-04 | 0029 | | 7-Day Safety Report | SP615 | | 2004-00274 | 11428 |
| 07-Jun-04 | 0030 | | Initial Safety Report | SP615 | | 2004-00266 | 10194 |
| 21-Jun-04 | 0031 | | Protocol Amendment: New Investigator | SP616 | New and revised investigators | | |
| 24-Jun-04 | 0032 | | Follow-up Safety Report | SP615 | | 2004-00266 | 10194 |
| 24-Jun-04 | 0032 | | Follow-up Safety Report | SP615 | | 2004-00274 | 11428 |
| 28-Jun-04 | 0033 | | Initial Safety Report | SP742 | | 2004-00326 | 15502/80010 |
| 28-Jun-04 | 0033 | | Initial Safety Report | SP743 | | 2004-00321 | 11406/8011 |
| 28-Jun-04 | 0034 | | Annual Report | | Period covering 15-OCT-2004 through 25-MAR-2004 | | |
| 01-Jul-04 | | | Initial Safety Report | SP742 | Fax 7-day safety reports to FDA | 2004-00356 | 13002/80062 |
| 01-Jul-04 | | | 7-Day Safety Report | SP743 | Fax 7-day safety reports to FDA | 2004-00355 | 12307 |
| 01-Jul-04 | 0035 | | Follow-up Safety Report | SP667 | | 2003-00298 | 11910/80301 |
| 01-Jul-04 | 0035 | | Follow-up Safety Report | SP615 | | 2004-00232 | 11478 |
| 01-Jul-04 | 0036 | | 7-Day Safety Report | SP743 | | 2004-00355 | 12307 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 01-Jul-04 | 0036 | | Initial Safety Report | SP742 | | 2004-00356 | 13002/80062 |
| 13-Jul-04 | 0037 | | Follow-up Safety Report | SP743 | | 2004-00355 | 12307/80040 |
| 13-Jul-04 | 0037 | | Follow-up Safety Report | SP742 | | 2004-00326 | 15502/80010 |
| 13-Jul-04 | 0038 | | Initial Safety Report | SP743 | | 2004-00366 | 12302/80036 |
| 14-Jul-04 | | | 7-Day Safety Report | SP743 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00380 | 15712/80094 |
| 14-Jul-04 | 0039 | | 7-Day Safety Report | SP743 | | 2004-00380 | 15712/80094 |
| 19-Jul-04 | 0040 | | Initial Safety Report | SP742 | | 2004-00370 | 13805/80082 |
| 21-Jul-04 | 0041 | | Information Amendment: Clinical | SP588 | Multiple dose tolerance study with ascending oral doses of SPM 927 (harkoseride) in healthy male caucasian volunteers | | |
| 21-Jul-04 | 0042 | | Follow-up Safety Report | SP742 | | 2004-00356 | 13002/80062 |
| 04-Aug-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00428 | 14309 |
| 04-Aug-04 | 0043 | | 7-Day Safety Report | SP742 | | 2004-00428 | 14309 |
| 05-Aug-04 | 0044 | | Follow-up Safety Report | SP615 | | 2004-00266 | 10194 |
| 05-Aug-04 | 0044 | | Follow-up Safety Report | SP743 | | 2004-00321 | 11406/80110 |
| 05-Aug-04 | 0044 | | Follow-up Safety Report | SP743 | | 2004-00380 | 15712/80094 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 05-Aug-04 | 0044 | | Follow-up Safety Report | SP615 | | 2004-00232 | 11478 |
| 09-Aug-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00441 | 15601/80177 |
| 09-Aug-04 | 0045 | | 7-Day Safety Report | SP742 | | 2004-00441 | 15601/80177 |
| 10-Aug-04 | 0046 | | Information Amendment: Clinical | | Revised investigator's brochure dated May 2004 | | |
| 12-Aug-04 | | | 7-Day Safety Report | SP743 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00447 | 17508/80301 |
| 12-Aug-04 | 0047 | | Follow-up Safety Report | SP742 | | 2004-00428 | 14309/80133 |
| 12-Aug-04 | 0047 | | Follow-up Safety Report | SP742 | | 2004-00370 | 13805/80082 |
| 12-Aug-04 | 0048 | | 7-Day Safety Report | SP743 | | 2004-00447 | 17508/80301 |
| 16-Aug-04 | 0049 | | Initial Safety Report | SP743 | | 2004-00443 | 16811/80194 |
| 23-Aug-04 | 0050 | | Follow-up Safety Report | SP743 | | 2004-00447 | 17508/80301 |
| 23-Aug-04 | 0050 | | Follow-up Safety Report | SP743 | | 2004-00443 | 16811/80194 |
| 23-Aug-04 | 0050 | | Follow-up Safety Report | SP743 | | 2004-00355 | 12307/80040 |
| 23-Aug-04 | 0050 | | Follow-up Safety Report | SP615 | | 2003-00323 | 10616/10538 |
| 24-Aug-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00483 | 15210/80059 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 24-Aug-04 | 0051 | | 7-Day Safety Report | SP742 | | 2004-00483 | 15210/80059 |
| 25-Aug-04 | 0052 | | Response to FDA Request for Information | SP742 | Respond to FDA request for follow-up information regarding this case; requested on 10-AUG-2004. | 2004-00356 | 13002/80062 |
| 30-Aug-04 | 0053 | | Follow-up Safety Report | SP742 | | 2004-00370 | 13805/80082 |
| 30-Aug-04 | 0053 | | Follow-up Safety Report | SP742 | | 2004-00356 | 13002/80062 |
| 02-Sep-04 | | | 7-Day Safety Report Fax | SP743 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00507 | 14919 |
| 02-Sep-04 | 0054 | | 7-Day Safety Report | SP743 | | 2004-00507 | 14919 |
| 09-Sep-04 | 0055 | | Follow-up Safety Report | SP615 | | 2004-00274 | 11428 |
| 09-Sep-04 | 0055 | | Follow-up Safety Report | SP743 | | 2004-00447 | 17508/80301 |
| 09-Sep-04 | 0055 | | Follow-up Safety Report | SP743 | | 2004-00443 | 16811/80194 |
| 09-Sep-04 | 0056 | | Meeting Request | | Schwarz requests end of phase 2 type B meeting to discuss clinical development program for the iv formulation. | | |
| 14-Sep-04 | | | FDA Phone Contact | | Ms. Griffis, FDA, calls to give end of phase 2 meeting date of 9-DEC-2004. | | |
| 14-Sep-04 | | | FDA Correspondence | | Ms. Giffis, FDA, emails date of 9-DEC-2004 for end of phase 2 meeting. | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 15-Sep-04 | | | General Correspondence | | Email Ms. Griffis, FDA, question on how the FDA will proceed with review of the CMC section. | | |
| 17-Sep-04 | | | FDA Correspondence | | Ms. Griffis, FDA, emails that once the briefing document is received she will have the chemist review it and determine if a meeting is needed. | | |
| 23-Sep-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00553 | 13308/80166 |
| 23-Sep-04 | 0057 | | 7-Day Safety Report | SP742 | | 2004-00553 | 13308/80166 |
| 27-Sep-04 | 0058 | | Initial Safety Report | SP742 | | 2004-00544 | 15803 |
| 27-Sep-04 | 0058 | | Initial Safety Report | SP742 | | 2004-00551 | 14609 |
| 29-Sep-04 | 0059 | | Follow-up Safety Report | SP742 | | 2004-00428 | 14309/80133 |
| 29-Sep-04 | 0059 | | Follow-up Safety Report | SP743 | | 2004-00507 | 14919 |
| 29-Sep-04 | 0059 | | Follow-up Safety Report | SP743 | | 2004-00443 | 16811/80194 |
| 08-Oct-04 | 0060 | | Initial Safety Report | SP615 | | 2004-00573 | 10529 |
| 13-Oct-04 | | | 7-Day Safety Report | SP615 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00580 | 10626 |
| 13-Oct-04 | 0061 | | 7-Day Safety Report | SP615 | | 2004-00580 | 10626 |
| 15-Oct-04 | | | 7-Day Safety Report | SP754 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00616 | 15605 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 15-Oct-04 | 0062 | | 7-Day Safety Report | SP754 | | 2004-00616 | 15605 |
| 19-Oct-04 | 0063 | | Follow-up Safety Report | SP754 | | 2004-00616 | 15605 |
| 19-Oct-04 | 0063 | | Follow-up Safety Report | SP742 | | 2004-00551 | 14609 |
| 19-Oct-04 | 0063 | | Follow-up Safety Report | SP742 | | 2004-00553 | 13308/80166 |
| 19-Oct-04 | 0063 | | Follow-up Safety Report | SP742 | | 2004-00544 | 15803 |
| 19-Oct-04 | 0063 | | Follow-up Safety Report | SP615 | | 2004-00573 | 10529 |
| 20-Oct-04 | | | FDA Correspondence | | Ms. Griffis, FDA, emails that the chemist is reviewing the package. | | |
| 21-Oct-04 | | | FDA Correspondence | | Ms. Griffis, FDA, emails that the CMC team does not need to attend the 57,939 meeting as she hope to have CMC questions answered soon. | | |
| 25-Oct-04 | 0064 | | Initial Safety Report | SP743 | | 2004-00614 | 17603/80422 |
| 26-Oct-04 | 0065 | | Meeting Package | | End of phase 2 meeting package for meeting scheduled 9-DEC-2004. | | |
| 01-Nov-04 | 0066 | | Follow-up Safety Report | SP743 | | 2004-00380 | 15712/80094 |
| 08-Nov-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00599 | 14004/80152 |
| 08-Nov-04 | 0067 | | 7-Day Safety Report | SP742 | | 2004-00599 | 14004/80152 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 10-Nov-04 | 0068 | | Initial Safety Report | SP615 | | 2004-00665 | 10402 |
| 12-Nov-04 | 0069 | | Follow-up Safety Report | SP742 | | 2004-00551 | 14609 |
| 12-Nov-04 | 0069 | | Follow-up Safety Report | SP742 | | 2004-00441 | 15601/80177 |
| 12-Nov-04 | 0069 | | Follow-up Safety Report | SP742 | | 2004-00326 | 15502/80010 |
| 29-Nov-04 | 0070 | | Follow-up Safety Report | SP742 | | 2004-00483 | 15210/80059 |
| 01-Dec-04 | 0071 | | Follow-up Safety Report | SP743 | | 2004-00614 | 17603/80422 |
| 01-Dec-04 | 0071 | | Follow-up Safety Report | SP742 | | 2004-00553 | 13308/80166 |
| 07-Dec-04 | 0072 | | Initial Safety Report | SP743 | | 2004-00742 | 17029//80430 |
| 15-Dec-04 | 0073 | | Follow-up Safety Report | SP615 | | 2004-00665 | 10402 |
| 21-Dec-04 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00791 | 14806/80389 |
| 21-Dec-04 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00790 | 112104/80001 |
| 21-Dec-04 | 0074 | | 7-Day Safety Report | SP768 | | 2004-00790 | 112104/80001 |
| 21-Dec-04 | 0074 | | 7-Day Safety Report | SP742 | | 2004-00791 | 14806/80389 |
| 22-Dec-04 | 0075 | | Follow-up Safety Report | SP743 | | 2004-00742 | 17029/80430 |
| 22-Dec-04 | 0076 | | Initial Safety Report | SP746 | | 2004-00778 | 17514 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 22-Dec-04 | 0076 | | Initial Safety Report | SP755 | | 2004-00785 | 11601/85761 |
| 28-Dec-04 | | | 7-Day Safety Report | SP755 | Fax Ms. Griffis, FDA, 7-day safety report | 2004-00815 | 106302/82234 |
| 28-Dec-04 | 0077 | | Protocol Amendment: New Protocol | SP757 | New Protocol | | |
| 28-Dec-04 | 0078 | | 7-Day Safety Report | SP755 | | 2004-00815 | 106302/82234 |
| 03-Jan-05 | | | FDA Correspondence | | Ms. Griffis, FDA, emails that the meeting minutes are circulating at FDA for comments and lists the FDA attendees | | |
| 03-Jan-05 | 0079 | | Follow-up Safety Report | SP755 | | 2004-00785 | 11601/85761 |
| 03-Jan-05 | 0079 | | Follow-up Safety Report | SP743 | | 2004-00742 | 17029/80430 |
| 03-Jan-05 | 0079 | | Follow-up Safety Report | SP615 | | 2004-00580 | 10626 |
| 06-Jan-05 | 0080 | | Information Amendment: CMC Data | | | | |
| 10-Jan-05 | 0081 | | Follow-up Safety Report | SP755 | | 2004-00785 | 11601/85761 |
| 10-Jan-05 | 0081 | | Follow-up Safety Report | SP768 | | 2004-00790 | 112104/80001 |
| 10-Jan-05 | 0081 | | Follow-up Safety Report | SP746 | | 2004-00778 | 17514 |
| 10-Jan-05 | 0081 | | Follow-up Safety Report | SP742 | | 2004-00599 | 14004/80152 |
| 13-Jan-05 | | | 7-Day Safety Report | SP755 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00008 | 122303/87995 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 13-Jan-05 | 0082 | | 7-Day Safety Report | SP755 | | 2005-00008 | 122303/87995 |
| 19-Jan-05 | 0083 | | SB Meeting Minutes | | Schwarz submits meeting minutes and related attachements from end of phase 2 meeting with FDA 9-DEC-2004. Requests FDA send meeting minutes to Schwarz. | | |
| 20-Jan-05 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00051 | 14243/80369 |
| 20-Jan-05 | 0084 | | Initial Safety Report | SP755 | | 2005-00015 | 110902/83890 |
| 20-Jan-05 | 0085 | | 7-Day Safety Report | SP742 | | 2005-00051 | 14243/80369 |
| 24-Jan-05 | 0086 | | 7-Day Safety Report | SP742 | | 2005-00059 | 12725/80373 |
| 24-Jan-05 | 0086 | | 7-Day Safety Report | SP742 | | 2005-00041 | 10911/80361 |
| 25-Jan-05 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00061 | 111307/80163 |
| 25-Jan-05 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00060 | 111305/80162 |
| 25-Jan-05 | 0087 | | 7-Day Safety Report | SP768 | | 2005-00061 | 111307/80163 |
| 25-Jan-05 | 0087 | | 7-Day Safety Report | SP768 | | 2005-00060 | 111305/80162 |
| 27-Jan-05 | 0088 | | Follow-up Safety Report | SP755 | | 2005-00008 | 122303/87995 |
| 28-Jan-05 | | | FDA Meeting Minutes | | FDA emails meeting minutes from 9-DEC-2004 end of phase 2 meeting | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 28-Jan-05 | 0089 | | Initial Safety Report | SP755 | | 2005-00049 | 118603/86661 |
| 01-Feb-05 | | | 7-Day Safety Report | SP755 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00077 | 10841/82989 |
| 01-Feb-05 | | | 7-Day Safety Report | SP742 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00088 | 14251/80421 |
| 01-Feb-05 | 0090 | | 7-Day Safety Report | SP742 | | 2005-00088 | 14251/80421 |
| 01-Feb-05 | 0090 | | 7-Day Safety Report | SP755 | | 2005-00077 | 10841/82989 |
| 02-Feb-05 | 0091 | | Follow-up Safety Report | SP768 | | 2005-00060 | 111305/80162 |
| 02-Feb-05 | 0091 | | Follow-up Safety Report | SP768 | | 2005-00061 | 111307/80163 |
| 02-Feb-05 | 0091 | | Follow-up Safety Report | SP755 | | 2005-00015 | 110902/83890 |
| 02-Feb-05 | 0091 | | Follow-up Safety Report | SP755 | | 2004-00785 | 116101/85761 |
| 04-Feb-05 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00096 | 112703/80093 |
| 04-Feb-05 | 0092 | | 7-Day Safety Report | SP768 | | 2005-00096 | 112703/80093 |
| 04-Feb-05 | 0093 | | Follow-up Safety Report | SP742 | | 2005-00041 | 10911/80361 |
| 04-Feb-05 | 0093 | | Follow-up Safety Report | SP742 | | 2005-00059 | 12725/80373 |
| 04-Feb-05 | 0093 | | Follow-up Safety Report | SP742 | | 2005-00051 | 14243/80369 |
| 09-Feb-05 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00119 | 110403/80108 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 09-Feb-05 | 0094 | | 7-Day Safety Report | SP768 | | 2005-00119 | 110403/80108 |
| 09-Feb-05 | 0095 | | Follow-up Safety Report | SP755 | | 2005-00049 | 118603/86661 |
| 10-Feb-05 | 0096 | | Initial Safety Report | SP768 | | 2005-00089 | 112909/80024 |
| 10-Feb-05 | 0096 | | Initial Safety Report | SP754 | | 2004-00454 | 15103/80069 |
| 14-Feb-05 | 0097 | | Follow-up Safety Report | SP615 | | 2004-00580 | 10626 |
| 14-Feb-05 | 0097 | | Follow-up Safety Report | SP768 | | 2005-00096 | 112703/80093 |
| 14-Feb-05 | 0097 | | Follow-up Safety Report | SP755 | | 2005-00077 | 108401/82989 |
| 14-Feb-05 | 0097 | | Follow-up Safety Report | SP742 | | 2004-00791 | 14806/80389 |
| 14-Feb-05 | 0097 | | Follow-up Safety Report | SP742 | | 2005-00088 | 14251/80421 |
| 15-Feb-05 | 0098 | | Follow-up Safety Report | SP615 | | 2004-00189 | 10185 |
| 17-Feb-05 | 0099 | | Protocol Amendment: New Investigator | SP757 | New investigator | | |
| 24-Feb-05 | 0100 | | Initial Safety Report | SP754 | | 2005-00160 | 16102/80118 |
| 24-Feb-05 | 0100 | | Initial Safety Report | SP615 | | 2004-00732 | 11280 |
| 01-Mar-05 | | | 7-Day Safety Report | SP746 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00170 | 14913 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 01-Mar-05 | | | 7-Day Safety Report | SP745 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00168 | 175210 |
| 01-Mar-05 | 0101 | | 7-Day Safety Report | SP745 | | 2005-00168 | 175210 |
| 01-Mar-05 | 0101 | | 7-Day Safety Report | SP746 | | 2005-00170 | 14913 |
| 03-Mar-05 | 0102 | | Follow-up Safety Report | SP742 | | 2005-00041 | 10911/80361 |
| 03-Mar-05 | 0102 | | Follow-up Safety Report | SP754 | | 2004-00454 | 15103/80069 |
| 04-Mar-05 | 0103 | | 7-Day Safety Report | SP755 | | 2005-00185 | 116407/85873 |
| 08-Mar-05 | 0104 | | Initial Safety Report | SP756 | | 2005-00177 | 15103 |
| 09-Mar-05 | 0105 | | 7-Day Safety Report | SP742 | | 2005-00193 | 12204/80337 |
| 11-Mar-05 | 0106 | | Initial Safety Report | SP743 | | 2004-00444 | 17805/80350 |
| 14-Mar-05 | 0107 | | Follow-up Safety Report | SP754 | | 2005-00160 | 16102/80118 |
| 14-Mar-05 | 0107 | | Follow-up Safety Report | SP745 | | 2005-00168 | 175210 |
| 17-Mar-05 | 0108 | | Protocol Amendment: New Investigator | SP757 | New investigators | | |
| 21-Mar-05 | 0109 | | Follow-up Safety Report | SP768 | | 2005-00089 | 112909/80024 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00380 | 15712/80094 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00366 | 12302/80036 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00355 | 12307/80040 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00443 | 16811/80194 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00321 | 11406/80110 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00447 | 17508/80301 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00742 | 17029/80430 |
| 23-Mar-05 | 0110 | | Follow-up Safety Report | SP743 | | 2004-00507 | 14919/80387 |
| 29-Mar-05 | 0111 | | Follow-up Safety Report | SP742 | | 2005-00193 | 12204/80337 |
| 29-Mar-05 | 0111 | | Follow-up Safety Report | SP755 | | 2005-00077 | 108401/82989 |
| 01-Apr-05 | 0112 | | Follow-up Safety Report | SP665 | | 2002-00306 | 10141/10141 |
| 01-Apr-05 | 0112 | | Follow-up Safety Report | SP755 | | 2005-00185 | 116407/85873 |
| 01-Apr-05 | 0112 | | Follow-up Safety Report | SP768 | | 2005-00119 | 110403/80108 |
| 04-Apr-05 | 0113 | | Initial Safety Report | SP615 | | 2005-00253 | 10476 |
| 12-Apr-05 | 0114 | | Follow-up Safety Report | SP746 | | 2005-00170 | 14913 |
| 14-Apr-05 | 0115 | | Follow-up Safety Report | SP755 | | 2005-00008 | 122303/87995 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 14-Apr-05 | 0115 | | Follow-up Safety Report | SP742 | | 2004-00428 | 14309/80133 |
| 25-Apr-05 | 0116 | | Follow-up Safety Report | SP746 | | 2005-00177 | 15103 |
| 25-Apr-05 | 0116 | | Follow-up Safety Report | SP746 | | 2005-00170 | 14913 |
| 26-Apr-05 | 0117 | | Protocol Amendment: New Investigator | SP757 | New investigators | | |
| 26-Apr-05 | 0118 | | Initial Safety Report | SP768 | | 2005-00303 | 101803/80331 |
| 02-May-05 | 0119 | | Follow-up Safety Report | SP768 | | 2005-00119 | 110403/80109 |
| 02-May-05 | 0119 | | Follow-up Safety Report | SP768 | | 2005-00303 | 101803/80331 |
| 02-May-05 | 0120 | | 7-Day Safety Report | SP755 | | 2005-00323 | 106406//82279 |
| 11-May-05 | 0121 | | Initial Safety Report | SP754 | | 2005-00341 | 16013/80206 |
| 11-May-05 | 0121 | | Initial Safety Report | SP830 | | 2005-00326 | 110503 |
| 18-May-05 | 0122 | | Follow-up Safety Report | SP615 | | 2005-00253 | 10476 |
| 20-May-05 | | | 7-Day Safety Report | SP768 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00375 | 109308/80117 |
| 20-May-05 | 0123 | | 7-Day Safety Report | SP768 | | 2005-00375 | 109308/80117 |
| 24-May-05 | 0124 | | Initial Safety Report | SP768 | | 2005-00358 | 108702/80471 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 24-May-05 | 0124 | | Initial Safety Report | SP754 | | 2005-00370 | 12804/80207 |
| 26-May-05 | 0125 | | Information Amendment: Pharmacology/Toxicology | LPT 13124/00 | 104-week carcinogenicity study of SPM 927 by oral administration to CD-1 mice | | |
| 26-May-05 | 0125 | | Information Amendment: Pharmacology/Toxicology | LPT 13295/00 | 104-week carcinogenicity study of SPM 927 by oral administration to CD-1 rats | | |
| 27-May-05 | | | 7-Day Safety Report | SP746 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00011 | 15009 |
| 27-May-05 | 0126 | | Follow-up Safety Report | SP755 | | 2005-00077 | 108401/82989 |
| 27-May-05 | 0126 | | Follow-up Safety Report | SP742 | | 2005-00193 | 12204/80337 |
| 27-May-05 | 0127 | | 7-Day Safety Report | SP746 | | 2005-00011 | 15009 |
| 01-Jun-05 | 0128 | | Protocol Amendment: Change in Protocol | SP757 | Amendment 1 | | |
| 02-Jun-05 | 0129 | | Information Amendment: Clinical | SP607 | An open label, dose ittration trial to determine tolerability and efficacy of oral SPM 927 as adjunctive therapy in patients with partial seizures with or without secondary generalization | | |
| 03-Jun-05 | 0130 | | Initial Safety Report | SP755 | | 2005-00405 | 110109/83605 |
| 03-Jun-05 | 0130 | | Initial Safety Report | SP746 | | 2005/00409 | 17014 |
| 06-Jun-05 | 0131 | | 7-Day Safety Report | SP768 | | 2005-00424 | 101410/80256 |
| 06-Jun-05 | 0132 | | Follow-up Safety Report | SP755 | | 2005-00323 | 106406/82279 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 07-Jun-05 | | | FDA Correspondence | | Ms. Griffis, FDA, provides contact information for Ms. Calder during her leave of absence | | |
| 15-Jun-05 | 0133 | | 7-Day Safety Report | SP768 | | 2005-00444 | 112305/80382 |
| 16-Jun-05 | 0134 | | Protocol Amendment: New Investigator | SP640 | New investigator | | |
| 16-Jun-05 | 0134 | | Protocol Amendment: New Protocol | SP640 | New protocol | | |
| 20-Jun-05 | 0135 | | Information Amendment: Clinical | | | | |
| 22-Jun-05 | 0136 | | Follow-up Safety Report | SP615 | | 2004-00580 | 10626 |
| 23-Jun-05 | 0137 | | Request FDA Comment | | Request biowaiver for in vivo bioequivalence study for syrup; submit core text of SP643 and SP658 | | |
| 23-Jun-05 | 0138 | | Initial Safety Report | SP746 | | 2005-00441 | 17415 |
| 24-Jun-05 | 0139 | | Follow-up Safety Report | SP768 | | 2005-00375 | 109308/80117 |
| 24-Jun-05 | 0139 | | Follow-up Safety Report | SP755 | | 2005-00405 | 110109/83605 |
| 24-Jun-05 | 0139 | | Follow-up Safety Report | SP746 | | 2005-00409 | 17014 |
| 24-Jun-05 | 0139 | | Follow-up Safety Report | SP768 | | 2005-00424 | 101410/80256 |
| 27-Jun-05 | 0140 | | Initial Safety Report | SP755 | | 2005-00206 | 108202/82918 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 27-Jun-05 | 0140 | | Initial Safety Report | SP615 | | 2005-00465 | 10477 |
| 27-Jun-05 | 0140 | | Initial Safety Report | SP756 | | 2005-00467 | 16005 |
| 27-Jun-05 | 0141 | | Protocol Amendment: New Investigator | SP757 | New investigators | | |
| 30-Jun-05 | 0142 | | Annual Report | | period covering 26-MAR-2004 through 25-MAR-2005 | | |
| 01-Jul-05 | 0143 | v1 p1 | Information Amendment: Clinical | 678-02 | Determination of SPM 927 and SPM 12809 in human plasma by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660) | | |
| 01-Jul-05 | 0143 | v1 p136 | Information Amendment: Clinical | 679-02 | Determination of SPM 927 and SPM 12809 in human urine by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660) | | |
| 01-Jul-05 | 0143 | v2 p1 | Information Amendment: Clinical | 680-02 | Determination of SPM 927 and SPM 12809 in human saliva by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660) | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 01-Jul-05 | 0143 | v2 p64 | Information Amendment: Clinical | 031/04-05.MN | Validation of a LC/MS/MS method for the determination of metformin concentrations in human plasma and human urine samples and application of the validated assays to routine analysis of plasma and urine samples of study SP660 | | |
| 06-Jul-05 | 0144 | | Follow-up Safety Report | SP768 | | 2005-00424 | 101410/80256 |
| 06-Jul-05 | 0144 | | Follow-up Safety Report | SP756 | | 2005-00444 | 112305/80382 |
| 06-Jul-05 | 0144 | | Follow-up Safety Report | SP768 | | 2005-00467 | 16005 |
| 07-Jul-05 | 0145 | | Information Amendment: Pharmacology/Toxicology | 750-03 | Determination of SPM 927 and SPM 12809 in rat plasma by HPLC electrospray MS after oral administration of lacosamide to juvenile rats in a dose-range-finding study (LPT 18601/04) | | |
| 08-Jul-05 | 0146 | | Information Amendment: Clinical | SP642 | Open, non-randomized, group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 twice daily in male and female subjects with hepatic impairment compared w/ male and female healthy subj following multiple-dose admin | | |
| 11-Jul-05 | | | FDA Correspondence | | FDA mails clarification letter to respond to a number of questions as a result of agency letter 16-MAR-2005 requesting possibly suicide related evaluation of AEs occuring in lacosamide trials | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 12-Jul-05 | | | FDA Correspondence | | FDA faxes clarification letter to respond to a number of questions as a result of agency letter 16-MAR-2005 requesting possibly suicide related evaluation of AEs occuring in lacosamide trials | | |
| 14-Jul-05 | 0147 | | Initial Safety Report | SP755 | | 2005-00493 | 106305/82237 |
| 14-Jul-05 | 0148 | | Follow-up Safety Report | SP768 | | 2005-00375 | 109308/80117 |
| 14-Jul-05 | 0148 | | Follow-up Safety Report | SP754 | | 2005-00341 | 16013/80206 |
| 14-Jul-05 | 0148 | | Follow-up Safety Report | SP615 | | 2004-00580 | 10626 |
| 18-Jul-05 | | | 7-Day Safety Report | SP830 | Fax Ms. Griffis, FDA, 7-day safety report | 2005-00211 | 108301 |
| 18-Jul-05 | 0149 | | Initial Safety Report | SP756 | | 2005-00512 | 15001 |
| 18-Jul-05 | 0149 | | Initial Safety Report | SP830 | | 2005-00492 | 112007 |
| 18-Jul-05 | 0150 | | 7-Day Safety Report | SP830 | | 2005-00211 | 108301 |
| 20-Jul-05 | 0151 | | Protocol Amendment: New Investigator | SP757 | Revised investigator | | |
| 20-Jul-05 | 0152 | | Follow-up Safety Report | SP830 | | 2005-00492 | 112007 |
| 21-Jul-05 | 0153 | | Follow-up Safety Report | SP755 | | 2005-00493 | 106305/82237 |
| 21-Jul-05 | 0153 | | Follow-up Safety Report | SP768 | | 2005-00444 | 112305/80382 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 21-Jul-05 | 0153 | | Follow-up Safety Report | SP746 | | 2005-00441 | 17415 |
| 25-Jul-05 | 0154 | | 7-Day Safety Report | SP768 | | 2005-00545 | 108808/80185 |
| 27-Jul-05 | 0155 | | Information Amendment: Clinical | SP586 | A phase II, multicenter, ascending dose assessment of the safety, tolerability, compatibility, efficacy, and pharmacokinetics of harkoseride (ADD 234037) as adjunctive therapy in patients with partial seizures | | |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00551 | 14609/80056 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00553 | 13308/80166 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00599 | 14004/80152 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00791 | 14806/80389 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2005-00041 | 10911/80361 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2005-00051 | 14243/80369 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2005-00059 | 12725/80373 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2005-00193 | 12204/80337 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00544 | 15803/80047 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00326 | 15502/80010 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2005-00088 | 14251/80421 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00441 | 15601/80177 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00428 | 14309/80133 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00370 | 13805/80082 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00356 | 13002/80062 |
| 28-Jul-05 | 0156 | | Follow-up Safety Report | SP742 | | 2004-00483 | 15210/80059 |
| 28-Jul-05 | 0157 | | Follow-up Safety Report | SP756 | | 2005-00512 | 15001 |
| 29-Jul-05 | 0158 | | 7-Day Safety Report | SP768 | | 2005-00556 | 106313/80468 |
| 29-Jul-05 | 0158 | | 7-Day Safety Report | SP768 | | 2005-00552 | 102704 |
| 29-Jul-05 | 0159 | | Initial Safety Report | SP768 | | 2005-00544 | 114721/80494 |
| 29-Jul-05 | 0159 | | Initial Safety Report | SP768 | | 2005-00533 | 103902 |
| 05-Aug-05 | 0160 | | Follow-up Safety Report | SP768 | | 2005-00545 | 108808/80185 |
| 05-Aug-05 | 0160 | | Follow-up Safety Report | SP768 | | 2005-00556 | 106313/80468 |
| 05-Aug-05 | 0160 | | Follow-up Safety Report | SP830 | | 2005-00211 | 108301 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 08-Aug-05 | 0161 | | Information Amendment: CMC Data | | Submit revised CMC information for drug substance and drug product with reference report PhTox 2678 | | |
| 10-Aug-05 | 0162 | | Initial Safety Report | SP746 | | 2005-00503 | 13706 |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | LPT 18772/05 | Determination of SPM 927, desmethyl-SPM 927 and desacetyl-SPM 927 concentrations in mouse plasma | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | LPT 18447/04 | Single dose pharmacokinetics of SPM 927 in CD®-1 mice | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 0699/025 | ( 14C)-SPM 927: Metabolism in hepatocytes isolated from mouse, rat, rabbit, dog and man | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 688 | Investigation of the metabolism of SPM 927 in different in vitro models | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 668 | Evaluation of the in vivo metabolism of SPM 927 to SPM 12809 in mice, rats and dogs following repeated oral administration of SPM 927 | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 0699/023 | ( 14C)-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat | | |
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 728 | Assessment of the systemic exposure to SPM 927, its desmethyl and its desacetyl metabolite in a single dose pharmacokinetic study of SPM 927 in male mice (188447/04, LPT) | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 10-Aug-05 | 0163 | | Information Amendment: Pharmacology/Toxicology | 750-03 | Determination of SPM 927 and SPM 12809 in rat plasma by HPLC-Electrospray MS after oral administration of lacosamide to juvenile rats in a dose-range-finding study (LPT 18601/04) | | |
| 15-Aug-05 | 0164 | | Information Amendment: Clinical | 606-03 | Re-validation of a solid-phase radioimmunoassay for determination of digoxin in human serum | | |
| 15-Aug-05 | 0164 | | Information Amendment: Clinical | 682-03 | Determination of SPM 927 in human plasma by HPLC Electrospray MS/MS after oral administration of SPM 927 (SP690) | | |
| 15-Aug-05 | 0164 | | Information Amendment: Clinical | 651 | Transport of SPM 927 across Caco-2 monolayer-Investigation of P-glycoprotein involvement | | |
| 15-Aug-05 | 0164 | | Information Amendment: Clinical | 607-03 | Re-validation of a solid-phase radioimmunoassay for determination of digoxin in human urine | | |
| 15-Aug-05 | 0165 | | 7-Day Safety Report | SP745 | | 2005-00597 | 111308 |
| 17-Aug-05 | 0166 | | Follow-up Safety Report | SP768 | | 2005-00545 | 108808/80185 |
| 17-Aug-05 | 0166 | | Follow-up Safety Report | SP746 | | 2005-00441 | 17415 |
| 17-Aug-05 | 0166 | | Follow-up Safety Report | SP768 | | 2005-00556 | 106313/80468 |
| 19-Aug-05 | 0167 | | Follow-up Safety Report | SP830 | | 2005-00211 | 108301 |
| 22-Aug-05 | 0168 | | Initial Safety Report | SP615 | | 2004-00543 | 10628 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 24-Aug-05 | 0169 | | Initial Safety Report | SP745 | | 2005-00527 | 170412 |
| 24-Aug-05 | 0169 | | Initial Safety Report | SP755 | | 2005-00602 | 124609/88827 |
| 24-Aug-05 | 0169 | | Initial Safety Report | SP830 | | 2005-00619 | 105619 |
| 25-Aug-05 | 0170 | | 7-Day Safety Report | SP745 | | 2005-00626 | 172706 |
| 26-Aug-05 | 0171 | | Follow-up Safety Report | SP768 | | 2005-00552 | 102704 |
| 29-Aug-05 | 0172 | | 7-Day Safety Report | SP768 | | 2005-00634 | 104610/80545 |
| 01-Sep-05 | 0173 | | Follow-up Safety Report | SP830 | | 2005-00619 | 105619 |
| 01-Sep-05 | 0173 | | Follow-up Safety Report | SP745 | | 2005-00626 | 172706 |
| 01-Sep-05 | 0174 | | Initial Safety Report | SP756 | | 2005-00635 | 11501 |
| 01-Sep-05 | 0174 | | Initial Safety Report | SP745 | | 2005-00631 | 111607 |
| 08-Sep-05 | 0175 | | Initial Safety Report | SP640 | | 2005-00636 | 82043 |
| 08-Sep-05 | 0175 | | Initial Safety Report | SP768 | | 2005-00643 | 109138 |
| 08-Sep-05 | 0176 | | Follow-up Safety Report | SP746 | | 2005-00503 | 13706 |
| 08-Sep-05 | 0176 | | Follow-up Safety Report | SP745 | | 2005-00631 | 111607 |
| 08-Sep-05 | 0176 | | Follow-up Safety Report | SP755 | | 2005-00323 | 106406/82279 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 08-Sep-05 | 0176 | | Follow-up Safety Report | SP745 | | 2005-00626 | 172706 |
| 13-Sep-05 | 0177 | | 7-Day Safety Report | SP863 | | 2005-00662 | 80011/80011 |
| 13-Sep-05 | 0178 | | Initial Safety Report | SP756 | | 2005-00649 | 12603 |
| 19-Sep-05 | 0179 | | Follow-up Safety Report | SP756 | | 2005-00635 | 11501 |
| 19-Sep-05 | 0179 | | Follow-up Safety Report | SP830 | | 2005-00619 | 105619 |
| 19-Sep-05 | 0179 | | Follow-up Safety Report | SP768 | | 2005-00634 | 104610/80545 |
| 19-Sep-05 | 0179 | | Follow-up Safety Report | SP755 | | 2005-00206 | 108202/82918 |
| 20-Sep-05 | 0180 | | Protocol Amendment: New Investigator | SP757 | New and revised investigators | | |
| 20-Sep-05 | 0181 | | Information Amendment: Clinical | SP645 | Randomized, open-label, single-dose, 2-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in healthy male subjects | | |
| 26-Sep-05 | 0182 | | Follow-up Safety Report | SP768 | | 2005-00544 | 114721/80494 |
| 26-Sep-05 | 0182 | | Follow-up Safety Report | SP768 | | 2005-00643 | 109138 |
| 26-Sep-05 | 0182 | | Follow-up Safety Report | SP768 | | 2005-00358 | 108702/80471 |
| 29-Sep-05 | 0183 | | Initial Safety Report | SP774 | | 2005-00648 | 104109 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 03-Oct-05 | 0184 | | Follow-up Safety Report | SP768 | | 2005-00552 | 102704 |
| 03-Oct-05 | 0184 | | Follow-up Safety Report | SP756 | | 2005-00649 | 12603 |
| 03-Oct-05 | 0184 | | Follow-up Safety Report | SP756 | | 2005-00467 | 16005 |
| 11-Oct-05 | 0185 | | Follow-up Safety Report | SP745 | | 2005-00527 | 170412 |
| 11-Oct-05 | 0185 | | Follow-up Safety Report | SP746 | | 2005-00503 | 13706 |
| 11-Oct-05 | 0185 | | Follow-up Safety Report | SP755 | | 2005-00602 | 124609/88827 |
| 11-Oct-05 | 0185 | | Follow-up Safety Report | SP756 | | 2005-00635 | 11501 |
| 11-Oct-05 | 0185 | | Follow-up Safety Report | SP830 | | 2005-00492 | 112007 |
| 13-Oct-05 | 0186 | | Initial Safety Report | SP830 | | 2005-00645 | 111205 |
| 20-Oct-05 | 0187 | | Protocol Amendment: New Investigator | SP757 | New and revised investigators | | |
| 26-Oct-05 | 0188 | | Follow-up Safety Report | SP830 | | 2005-00492 | 112007 |
| 26-Oct-05 | 0188 | | Follow-up Safety Report | SP755 | | 2005-00206 | 108202/82918 |
| 28-Oct-05 | 0189 | | 7-Day Safety Report | SP768 | | 2005-00744 | 108217/80452 |
| 01-Nov-05 | 0190 | | Follow-up Safety Report | SP755 | | 2005-00323 | 106406/82279 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 03-Nov-05 | 0191 | | Initial Safety Report | SP615 | | 2005-00738 | 11614 |
| 08-Nov-05 | 0192 | | Initial Safety Report | SP768 | | 2005-00750 | 104214 |
| 08-Nov-05 | 0192 | | Initial Safety Report | SP615 | | 2003-00367 | 11776 |
| 08-Nov-05 | 0193 | | Follow-up Safety Report | SP830 | | 2005-00645 | 111205 |
| 10-Nov-05 | 0194 | | General Correspondence | | Notify FDA of change in address and fax number | | |
| 16-Nov-05 | 0195 | | Follow-up Safety Report | SP745 | | 2005-00597 | 111308 |
| 16-Nov-05 | 0195 | | Follow-up Safety Report | SP830 | | 2005-00492 | 112007 |
| 22-Nov-05 | 0196 | | Initial Safety Report | SP754 | | 2005-00775 | 12512/80299 |
| 30-Nov-05 | 0197 | | Information Amendment: Clinical | SP690 | An open-label follow-on trial to assess the long-term safety and efficacy of oral SPM 927 in subjects with postherpetic neuralgia (PHN) | | |
| 30-Nov-05 | 0197 | | Information Amendment: Clinical | SP611 | An open-label trial to assess the efficacy and safety of ascending doses of SPM 927 in subjects with chronic refractory neuropathic pain | | |
| 02-Dec-05 | 0198 | | General Correspondence | | Request finalized list of FDA attendees and anticipated date of preliminary response to questions submitted in pre-NDA meeting package (Serial No. 0325); submit list of Schwarz attendees | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 05-Dec-05 | 0199 | | Follow-up Safety Report | SP768 | | 2005-00096 | 112703/80093 |
| 07-Dec-05 | 0200 | | Initial Safety Report | SP774 | | 2005-00803 | 110505/83749 |
| 08-Dec-05 | 0201 | | Follow-up Safety Report | SP863 | | 2005-00662 | 80011/80011 |
| 13-Dec-05 | 0202 | | Response to FDA Request for Information | | Submit information requested by Dr. Broadbent, FDA, for verification that both the masking agent and the strawberry flavoring are Generally Recognized as Safe (GRAS) | | |
| 14-Dec-05 | 0203 | | Follow-up Safety Report | SP615 | | 2005-00465 | 10477 |
| 14-Dec-05 | 0203 | | Follow-up Safety Report | SP768 | | 2005-00552 | 102704 |
| 15-Dec-05 | 0204 | | Initial Safety Report | SP830 | | 2005-00821 | 110604 |
| 19-Dec-05 | 0205 | | Follow-up Safety Report | SP768 | | 2005-00060 | 111305/80162 |
| 19-Dec-05 | 0205 | | Follow-up Safety Report | SP615 | | 2005-00253 | 10476 |
| 20-Dec-05 | 0206 | | Initial Safety Report | SP745 | | 2005-00827 | 108112 |
| 21-Dec-05 | 0207 | | Follow-up Safety Report | SP774 | | 2005-00803 | 110505/83749 |
| 21-Dec-05 | 0208 | | Protocol Amendment: New Investigator | SP757 | New investigator | | |
| 27-Dec-05 | 0209 | | 7-Day Safety Report | SP830 | | 2005-00843 | 115201 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 03-Jan-06 | 0210 | | Initial Safety Report | SP774 | | 2005-00834 | 122105 |
| 03-Jan-06 | 0210 | | Initial Safety Report | SP745 | | 2005-00848 | 109209 |
| 09-Jan-06 | 0211 | | Follow-up Safety Report | SP830 | | 2005-00821 | 110604 |
| 09-Jan-06 | 0212 | | Request FDA Comment | 754, SP755, SP6 | Submit proposed statistical analysis plan for protocol SP754 which may also apply to all double-blind trials in support of the treatment of epilepsy | | |
| 09-Jan-06 | 0213 | v1 | Information Amendment: Clinical | SP616 | A mutlicenter, double-blind, double-dummy, randomized trial to investigate the safety, tolerability and pharmacokinetics of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization | | |
| 09-Jan-06 | 0213 | v2 | Information Amendment: Clinical | SP661 | Randomized, double-blind, placebo-controlled, parallel-group, Phase 1 trial to evaluate the pharmacokinetics, safety, and tolerability following multiple-dose oral treatment of 200mg SPM 927 in healthy male White, Black, and Asian subjects | | |
| 09-Jan-06 | 0213 | v2 p249 | Information Amendment: Clinical | SP665 | An open-label follow-on trial to assess the long-term safety and efficacy of oral SPM 927 in subjects with diabetic neuropathy | | |
| 13-Jan-06 | 0214 | | 7-Day Safety Report | SP746 | | 2005-00400 | 16304 |
| 16-Jan-06 | 0215 | | Follow-up Safety Report | SP640 | | 2005-00636 | 82043 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 16-Jan-06 | 0215 | | Follow-up Safety Report | SP745 | | 2005-00848 | 109209 |
| 16-Jan-06 | 0215 | | Follow-up Safety Report | SP745 | | 2005-00827 | 108112 |
| 17-Jan-06 | | | 7-Day Safety Report Fax | SP745 | | 2006-00017 | 104902 |
| 17-Jan-06 | | | General Correspondence | SP768 | Email Ms. Calder, Ms. Griffis, and Ms. Malandro, FDA, notification that Schwarz will be submitting safety information | | |
| 17-Jan-06 | 0216 | | General Correspondence | SP768 | Submit safety update | | |
| 17-Jan-06 | 0217 | | 7-Day Safety Report | SP745 | | 2005-00017 | 104902 |
| 18-Jan-06 | 0218 | | 7-Day Safety Report | SP745 | | 2006-00019 | 104910 |
| 20-Jan-06 | | | General Correspondence | SP768 | Email Ms. Malandro and Ms. Calder, FDA, outlier analysis for SP768 submitted 20-JAN-2006 | | |
| 20-Jan-06 | | | FDA Correspondence | SP768 | Ms. Calder, FDA, confirms receipt of email containing outlier analysis for SP768 | | |
| 20-Jan-06 | 0219 | | 7-Day Safety Report | SP615 | | 2005-00031 | 11522 |
| 20-Jan-06 | 0220 | | Protocol Amendment: New Investigator | SP767 | New and revised investigators | | |
| 20-Jan-06 | 0221 | | General Correspondence | SP768 | Submit outlier analysis of SP768 | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 23-Jan-06 | | | FDA Correspondence | 754, SP755, SP€ | Ms. Calder, FDA, emails comment from statistical team regarding proposed statistical analysis plan submitted 9-JAN-2006 | | |
| 23-Jan-06 | 0222 | | General Correspondence | SP768 | Submit IDMC data for 24-JAN-2006 teleconference (rescheduled to 27-JAN-2006 at 1:30pm) | | |
| 24-Jan-06 | 0223 | | Follow-up Safety Report | SP754 | | 2005-00370 | 12804/80207 |
| 24-Jan-06 | 0223 | | Follow-up Safety Report | SP774 | | 2005-00834 | 122105 |
| 01-Feb-06 | 0224 | | Response to FDA Request for Information | , SP746, SP830, | Submit minutes from IDMC closed session on 31-JAN-2006 and report how Schwarz is responding to IDMC's conclusions | | |
| 02-Feb-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that the Division may want to meet in the future but the medical team is still reviewing information submitted 1-FEB-2006 | | |
| 02-Feb-06 | | | General Correspondence | | Email Ms. Calder, FDA, to ask if Division of Neurology Products is considering meeting over information provided 1-FEB-2006 | | |
| 03-Feb-06 | | | FDA Phone Contact | | Ms. Calder, FDA, calls to notify of a 6-FEB-2006 teleconference from 3:00-4:00pm to discuss safety information for lacosamide including the data submitted 17-JAN-2006 and 1-FEB-2006 | | |
| 06-Feb-06 | | | SB Meeting Minutes | | SB draft meeting minutes from 06-FEB-2006 teleconference | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 06-Feb-06 | | | General Correspondence | | Email Ms. Calder, FDA, to confirm 6-FEB-2006 teleconference and confirm conference call number and conference code | | |
| 07-Feb-06 | 0225 | | Follow-up Safety Report | SP745 | | 2005-00631 | 111607 |
| 07-Feb-06 | 0225 | | Follow-up Safety Report | SP774 | | 2005-00834 | 122105 |
| 08-Feb-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails report of delayed email | | |
| 10-Feb-06 | 0226 | | Information Amendment: Clinical | SP598, SP660 | | | |
| 10-Feb-06 | 0227 | | Initial Safety Report | SP774 | | 2006-00074 | 2006-00074 |
| 10-Feb-06 | 0227 | | Initial Safety Report | SP746 | | 2006-00056 | 14801 |
| 16-Feb-06 | 0228 | | Follow-up Safety Report | SP746 | | 2005-00400 | 16304 |
| 16-Feb-06 | 0228 | | Follow-up Safety Report | SP774 | | 2005-00834 | 122105 |
| 16-Feb-06 | 0228 | | Follow-up Safety Report | SP745 | | 2006-00019 | 104910 |
| 17-Feb-06 | 0229 | | Request FDA Comment | | Submit revised Informed Consent Form for review | | |
| 21-Feb-06 | 0230 | | Protocol Amendment: New Investigator | SP757 | New and revised investigators | | |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00556 | 106313/80468 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00750 | 104214/80312 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00744 | 108217/80452 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00375 | 109308/80117 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00089 | 112909/80024 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00424 | 101410/80256 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00119 | 110403/80108 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00545 | 108808/80185 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00533 | 103902/80631 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00544 | 114721/80494 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00096 | 112703/80093 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00444 | 112305/80382 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2004-00790 | 112104/80001 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00358 | 108702/80471 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00061 | 111307/80163 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00552 | 102704/80359 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00634 | 104610/80545 |
| 23-Feb-06 | 0231 | | Follow-up Safety Report | SP768 | | 2005-00643 | 109138/80573 |
| 27-Feb-06 | 0232 | | 7-Day Safety Report | SP830 | | 2005-00644 | 105616 |
| 28-Feb-06 | 0233 | | 7-Day Safety Report | SP745 | | 2006-00114 | 106316 |
| 01-Mar-06 | 0234 | | Follow-up Safety Report | SP774 | | 2006-00074 | 110405 |
| 01-Mar-06 | 0234 | | Follow-up Safety Report | SP774 | | 2005-00803 | 110505/83749 |
| 01-Mar-06 | 0234 | | Follow-up Safety Report | SP745 | | 2005-00597 | 111308 |
| 03-Mar-06 | 0235 | | General Correspondence | | Request FDA review and comment on revised IB and ICF | | |
| 07-Mar-06 | | | General Correspondence | | Email Ms. Calder, FDA, about status of review of the IB and ICF for lacosamide | | |
| 08-Mar-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that she did not receive electronic copy of 03-MAR-2006 IB and ICF submission | | |
| 08-Mar-06 | | | General Correspondence | | Email Ms. Calder, FDA, first half of 03-MAR-2006 IB and ICF submission | | |
| 08-Mar-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails successful receipt of electronic copy of 03-MAR-2006 IB and ICF submission | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 08-Mar-06 | | | General Correspondence | | CC Ms. Calder email copy of 03-MAR-2006 IB and ICF submission | | |
| 08-Mar-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that the Division has not yet seen 03-MAR-2006 IB and ICF submission | | |
| 08-Mar-06 | | | General Correspondence | | Email Ms. Calder, FDA, submission details for 03-MAR-2006 IB and ICF submission | | |
| 08-Mar-06 | | | General Correspondence | | Email Ms. Calder, FDA, second half of 03-MAR-2006 IB and ICF submission | | |
| 15-Mar-06 | 0236 | | Initial Safety Report | SP830 | | 2006-00129 | 115104 |
| 15-Mar-06 | 0237 | | Follow-up Safety Report | SP774 | | 2005-00803 | 110505/83749 |
| 15-Mar-06 | 0237 | | Follow-up Safety Report | SP746 | | 2006-00056 | 14801 |
| 20-Mar-06 | 0238 | | Protocol Amendment: New Investigator | SP757 | New investigators | | |
| 21-Mar-06 | 0239 | | Follow-up Safety Report | SP830 | | 2005-00644 | 105616 |
| 29-Mar-06 | 0240 | | Information Amendment: Pharmacology/Toxicology | LPT 78604/02 | 6-Week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats - age at start of administration: 7 days | | |
| 31-Mar-06 | | | 7-Day Safety Report Fax | | Fax 31-Mar-2006 7-day safety report to Division | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 31-Mar-06 | 0241 | | 7-Day Safety Report | SP757 | | 2006-00158 | 170106 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00602 | 124609/88827 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00405 | 110109/83605 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00323 | 106406/82273 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00206 | 108202/82918 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00077 | 108401/82989 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2005-00008 | 122303/87995 |
| 05-Apr-06 | 0242 | | Follow-up Safety Report | SP755 | | 2004-00785 | 11601/85761 |
| 06-Apr-06 | 0243 | | 7-Day Safety Report | SP757 | | 2006-00166 | 170111 |
| 06-Apr-06 | 0244 | | Initial Safety Report | SP774 | | 2006-00161 | 108404/8292 |
| 13-Apr-06 | 0245 | | Initial Safety Report | SP830 | | 2006-00163 | 101109 |
| 14-Apr-06 | 0246 | | Meeting Request | | Request Type B Pre-NDA meeting with Division of Neurology Products | | |
| 20-Apr-06 | 0247 | | Protocol Amendment: New Investigator | SP757 | New investigators | | |
| 20-Apr-06 | 0248 | | Follow-up Safety Report | SP745 | | 2006-00114 | 106316 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 20-Apr-06 | 0248 | | Follow-up Safety Report | SP757 | | 2006-00158 | 170106 |
| 20-Apr-06 | 0248 | | Follow-up Safety Report | SP757 | | 2006-00166 | 170111 |
| 21-Apr-06 | 0249 | | General Correspondence | | Submit cardiovascular analysis, as requested in 6-FEB-2006 teleconference with the division | | |
| 24-Apr-06 | | | FDA Correspondence | SP757 | Ms. Calder, FDA, emails to report subject number for adverse event report referenced in same-day email | 2006-00158 | 170106 |
| 24-Apr-06 | | | FDA Correspondence | SP757 | Ms. Calder, FDA, emails questions about adverse event report and asks that Schwarz examine possible causality to medication and adequacy of cardiac monitoring during infusion | 2006-00158 | 170106 |
| 25-Apr-06 | 0250 | | General Correspondence | 40724/1 | Submit rationale and draft protocols for juvenile dog studies for FDA review and comment | | |
| 25-Apr-06 | 0250 | | General Correspondence | 40724/2 | Submit rationale and draft protocols for juvenile dog studies for FDA review and comment | | |
| 26-Apr-06 | 0251 | | Initial Safety Report | SP774 | | 2006-00066 | 124406 |
| 27-Apr-06 | 0252 | | Initial Safety Report | SP745 | | 2005-00598 | 172207 |
| 27-Apr-06 | 0253 | | Follow-up Safety Report | SP774 | | 2006-00161 | 108404/8292 |
| 27-Apr-06 | 0253 | | Follow-up Safety Report | SP830 | | 2006-00163 | 101109 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 28-Apr-06 | | | General Correspondence | SP757 | Email Ms. Calder, FDA, preliminary response to 24-APRIL-2006 email requesting additional safety information | 2006-00158 | 170106 |
| 01-May-06 | 0254 | | General Correspondence | SP757 | Submit requested safety information | 2006-00158 | 170106 |
| 03-May-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails additional request for suicidality data | | |
| 03-May-06 | 0255 | | Initial Safety Report | SP756 | | 2006-00186 | 12202 |
| 05-May-06 | 0256 | | Information Amendment: Clinical | SP641 | Open, non-randomized, sequential group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 in m&f subj. with renal impairment incl. subj. requiring dialysis compared with m&f healthy subj. following single-dose admin. | | |
| 11-May-06 | 0257 | | General Correspondence | | Submit narratives for cardiovascular analysis | | |
| 12-May-06 | | | General Correspondence | | Email Ms. Calder, FDA, to request status of the review of draft protocols submitted 25-APR-2006 | | |
| 15-May-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that toxicology reviewer will not review 25-APR-2006 draft protocols for a few weeks | | |
| 15-May-06 | | | General Correspondence | | Email Ms. Calder, FDA, to ask if a toxicologist will be reviewing 25-APR-2006 draft protocols | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 15-May-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that the 25-APR-2006 draft protocols have not been reviewed yet but would be within the next week | | |
| 15-May-06 | | | General Correspondence | | Email Ms. Calder, FDA, to ask about status of draft toxicology studies | | |
| 15-May-06 | | | FDA Correspondence | | Ms. Calder, FDA, emails that the reviewer of IB hopes to have comments within the week | | |
| 15-May-06 | | | General Correspondence | | Email Ms. Calder, FDA, thanks for information on review timeline for 25-APR-2006 draft toxicology protocol submission | | |
| 18-May-06 | 0258 | | Initial Safety Report | SP774 | | 2006-00032 | 110406 |
| 18-May-06 | 0258 | | Initial Safety Report | SP754 | | 2006-00209 | 14312/80405 |
| 19-May-06 | 0259 | | Protocol Amendment: New Investigator | SP757 | New and revised investigators | | |
| 22-May-06 | 0260 | | Follow-up Safety Report | SP754 | | 2005-00775 | 12512/80299 |
| 22-May-06 | 0260 | | Follow-up Safety Report | SP830 | | 2006-00129 | 115104 |
| 22-May-06 | 0260 | | Follow-up Safety Report | SP830 | | 2005-00644 | 105616 |
| 22-May-06 | 0260 | | Follow-up Safety Report | SP745 | | 2005-00598 | 172207 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 26-May-06 | 0261 | | Information Amendment: Clinical | SP743 | A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day and 600mg/day SPM 927 in subjects with painful distal diabetic neuropathy | | |
| 26-May-06 | 0261 | | Information Amendment: Clinical | SP742 | A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 200, 400, and 600mg/day SPM 927 in subjects with painful distal neuropathy | | |
| 30-May-06 | 0262 | | Protocol Amendment: Change in Protocol | SP756 | Amendment 2 | | |
| 30-May-06 | 0262 | | Protocol Amendment: Change in Protocol | SP754 | Amendment 2 | | |
| 30-May-06 | 0262 | | Protocol Amendment: Change in Protocol | SP615 | Amendment 8 | | |
| 01-Jun-06 | 0263 | | Follow-up Safety Report | SP774 | | 2006-00032 | 110406 |
| 01-Jun-06 | 0263 | | Follow-up Safety Report | SP830 | | 2006-00129 | 115104 |
| 02-Jun-06 | 0264 | | General Correspondence | SP755 | Schwarz submits additional information requested by Calder, FDA, on 24-Apr-2006. Send revised narrative, cardiology consult reports and ECG reports | 2006-00158 | 170106 |
| 16-Jun-06 | 0265 | | Meeting Package | | Submit meeting package for 19-JUL-2006 Pre-NDA Meeting | | |
| 23-Jun-06 | 0266 | | Annual Report | | Period covering March 26, 2005 through March 25, 2006 | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 12-Jul-06 | 0267 | | Follow-up Safety Report | SP830 | | 2006-00129 | 115104 |
| 18-Jul-06 | 0268 | | 7-Day Safety Report | SP745 | | 2006-00284 | 172723 |
| 18-Jul-06 | 0268 | | 7-Day Safety Report | SP745 | | 2006-00283 | 172719 |
| 20-Jul-06 | 0269 | | Protocol Amendment: New Investigator | SP767 | Revised investigators | | |
| 25-Jul-06 | 0270 | | 7-Day Safety Report | SP745 | | 2006-00289 | 108305 |
| 31-Jul-06 | 0271 | | SB Meeting Minutes | | Submit Pre-NDA Meeting Minutes from meeting held 19-JULY-2006 | | |
| 02-Aug-06 | | | General Correspondence | | Mail to Dr. Levin, FDA, Type C meeting request with DNP, DAARP, and Office of Information Management to reach consesnuse with regard to technical aspects of filing lacosamide NDA | | |
| 02-Aug-06 | 0272 | | General Correspondence | | Submit Type C meeting request with DNP, DAARP, and Office of Information Management to reach consesnuse with regard to technical aspects of filing lacosamide NDA | | |
| 07-Aug-06 | 0273 | | Initial Safety Report | SP756 | | 2006-00295 | 18906 |
| 07-Aug-06 | 0273 | | Initial Safety Report | SP830 | | 2006-00293 | 10118 |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | A27033 | SPM 927: Toxicity to activated sludge in a respiration inhibition test | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | A22184 | SPM 927: Toxicity to scenedesmus subspicatus in a 72-hour algal growth inhibition test | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | A22206 | Adsorption/desorption of [14C]-SPM 927 on soils | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | F104017 | Assessment of SPM 927 in the SOD1 transgenic mouse model of ALS | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | A22173 | SPM 927: Ready biodegradability in a CO2 evolution (modified Sturm) test | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | F9696 | Evaluation of SPM 927 and SPM 14221 in an animal model of fibromyalgia | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | RS211 | Assessment of the dependence potential of SPM 927 in rats and dogs after chronic administration and abrupt withdrawal | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | F9664 | Effects of SPM 927 (harkoseride) on the development of amygdala kindling in rats | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | 03.488/5 | Evaluation of lacosamide, lamotrigine, levetiracetam, pregabalin, amitryptiline and venlafaxine in a model of neuropathic pain (Chung) in the rat (i.p. administration) | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | 10263 | In vitro pharmacology – receptor binding assay with SPM 927 and SPM 12809 | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | 05.122/6 | Evaluation of SPM 927 in the conditioned place preference test in the rat | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | AA24877 | Effects of SPM 927 (0.3, 1 and 3 mg/kg) on harmaline-induced tremors in rats | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | E-006-05-04 | Electrophysiological effects of SPM 12809 on the current mediated by the SCN5A-sodium channel stably expressed in CHO-K1 cells | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | 732 | Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | LPT 18601/04 | 6-week dose-range-finding study for a 6-week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats – age at start of administration: 7 days | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | LPT 18602/04 | 6-week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats – age at start of administration: 7 days | | |
| 10-Aug-06 | 0274 | | Information Amendment: Pharmacology/Toxicology | NRO 217.27.275. | Neuroprotective effect of SPM 927 on traumatic brain injury in rat | | |
| 10-Aug-06 | 0275 | | Follow-up Safety Report | SP745 | | 2005-00597 | 111308 |
| 16-Aug-06 | 0276 | | Follow-up Safety Report | SP774 | | 2006-00161 | 108406/8292 |
| 21-Aug-06 | 0277 | | Protocol Amendment: New Investigator | SP757 | Revised investigators | | |
| 22-Aug-06 | 0278 | | 7-Day Safety Report | SP830 | | 2006-00278 | 112204 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 24-Aug-06 | 0279 | | Follow-up Safety Report | SP745 | | 2006-00289 | 108305 |
| 24-Aug-06 | 0279 | | Follow-up Safety Report | SP756 | | 2006-00295 | 18906 |
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP658 | Randomized, open-label, single-dose, 3-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in 24 healthy male subjects | | |
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP863 | Open-label multiple-dose trial to evaluate the pharmacokinetic effect of lacosamide on omeprazole and vice versa in healthy male White subjects | | |
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP657 | Randomized, open, 2-period crossover trial to show bioequivalence following single oral dosing of a tablet and of a liquid of 200mg SPM 927 each in healthy subjects | | |
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP644 | Double-blind, placebo-controlled, randomized crossover Phase I trial to investigate a possible influence of SPM 927 on the steady state pharmacokinetics, pharmacodynamics, safety and tolerability of digoxin in healthy male Caucasian subjects | | |
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP643 | Randomized, open-label, two-way crossover trial to investigate the pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (CYP 2C19) | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 25-Aug-06 | 0280 | | Information Amendment: Clinical | SP599 | A study of the potential pharmacodynamic and pharmacokinetic interaction of SPM 927 (harkoseride) with Microgyn® in healthy female subjects | | |
| 28-Aug-06 | 0281 | | Request FDA Comment | SP903 | Request comment on abuse liability plan | | |
| 01-Sep-06 | 0282 | | 7-Day Safety Report | SP745 | | 2006-00350 | 101802 |
| 01-Sep-06 | 0282 | | 7-Day Safety Report | SP745 | | 2006-00357 | 175702 |
| 01-Sep-06 | 0283 | | Information Amendment: Clinical | | Submit Investigator's Brochure dated 29-AUG-2006 | | |
| 06-Sep-06 | | | SB Meeting Minutes | | Schwarz internal summary of 06-OCT-2006 meeting with the FDA to discuss lacosamide electronic submission issues | | |
| 07-Sep-06 | 0284 | | Follow-up Safety Report | SP774 | | 2006-00161 | 108406/8292 |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | Marzin-Lille | Expert report on the mutagenicity of SPM 927 | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | LPT 17962/04 | 28-Day immunotoxicological study of SPM 927 by repeated oral administration to CD-1 mice – plaque forming colony (PFC) test | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 6842-103 | Rising dose tolerance oral (capsule) toxicity study of ADD 234037 in dogs | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | LPT 17964/04 | Acute toxicity study of SPM 927 by single oral administration to CD rats | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | Olney | Evaluation of the potential of SPM 927 to induce acute neurotoxic changes in the adult rat brain | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | S03311 | An efficacy study of SPM 927 in a rat mammary tumor-induced bone pain model | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | SCHW 002 | Evaluation of SPM 927 in an animal model for anxiety: stress-induced hyperthermia | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 00704 | Therapeutic effect of SPM 927 in painful osteoarthritis in the rat | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 00649 | Effect of SPM 927 in ddC-induced painful neuropathy in the rat | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 00580 | Therapeutic effect of test compounds in painful diabetic neuropathy in the rat | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 00575 | Effect of SPM 927 in vincristine-induced painful neuropathy in the rat | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 507/511 | Effect of SPM 927 in two animal models of anxiety | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 505 | Effect of SPM 927 in an animal model for mania | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | AA20234 | Effects of SPM 927 on harmaline-induced tremors in rats | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 04.064/3 | Evaluation of SPM 927 in a model of visceral pain in the rat | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | LPT 17963/04 | Acute toxicity study of SPM 927 by single intravenous administration to CD-1 mice | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 8540 | In vitro pharmacology: GABA transaminase assay | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | SCHW001 | Evaluation of SPM 927 alone and in combination with clozapine on the prepulse inhibition of the startle response in C56/BL6 mice | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | 04.270/3 | Evaluation of SPM 927 in the behavioral despair test in the rat (i.p. administration) | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | AA19072 | Effects of SPM 927 on reserpine-induced tardive dyskinesia in mice | | |
| 12-Sep-06 | 0285 | | Information Amendment: Pharmacology/Toxicology | Krishtal | Electrophysiological characterization of SPM-927 | | |
| 15-Sep-06 | 0286 | | Initial Safety Report | SP774 | | 2006-00366 | 104504 |
| 15-Sep-06 | 0287 | | Follow-up Safety Report | SP830 | | 2006-00278 | 112204 |
| 15-Sep-06 | 0287 | | Follow-up Safety Report | SP745 | | 2006-00357 | 175702 |
| 18-Sep-06 | | | General Correspondence | SP903 | Email Ms. Calder, FDA, to request she follow up with CSS about timeline for response to 28-AUG-2006 abuse liability protocol submission | | |
| 19-Sep-06 | | | FDA Correspondence | SP903 | Ms. Calder, FDA, emails that CSS has completed its review of the abuse liability protocol and will send comments soon | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 19-Sep-06 | | | General Correspondence | SP903 | Email Ms. Calder, FDA, thanks for following up with CSS on abuse liability protocol review | | |
| 20-Sep-06 | | | General Correspondence | SP903 | Email Ms. Calder, FDA, thanks for recommendations regarding the abuse liability protocol | | |
| 20-Sep-06 | | | General Correspondence | | Email Ms. Calder, FDA, for feedback on questions in cover letter of abuse liability submission | | |
| 20-Sep-06 | | | FDA Correspondence | SP903 | Ms. Calder, FDA, emails 'you're welcome' for recommendations regarding the abuse liability protocol | | |
| 20-Sep-06 | | | FDA Correspondence | SP903 | Ms. Calder, FDA, emails recommendations regarding the abuse liability protocol | | |
| 20-Sep-06 | 0288 | | Protocol Amendment: New Investigator | SP757 | Revised investigator | | |
| 26-Sep-06 | 0289 | | 7-Day Safety Report | SP745 | | 2006-00389 | 170304 |
| 03-Oct-06 | | | FDA Meeting Minutes | | Ms. Calder, FDA, emails meeting minutes from 06-SEP-2006 meeting to discuss the electronic submission of multiple NDAs with multiple indications | | |
| 10-Oct-06 | 0290 | | Follow-up Safety Report | SP745 | | 2006-00389 | 170304 |
| 16-Oct-06 | 0291 | | Initial Safety Report | SP874 | | 2006-00403 | 125009/80029 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 16-Oct-06 | 0292 | | 7-Day Safety Report | SP745 | | 2005-00509 | 171324 |
| 19-Oct-06 | 0293 | | Initial Safety Report | SP774 | | 2006-00409 | 122402 |
| 19-Oct-06 | 0294 | | Follow-up Safety Report | SP754 | | 2005-00370 | 12804/80207 |
| 23-Oct-06 | 0295 | | 7-Day Safety Report | SP830 | | 2006-00420 | 105309 |
| 23-Oct-06 | 0296 | | General Correspondence | SP903 | Submit Protocol SP903 integrating comments from CSS | | |
| 25-Oct-06 | 0297 | | 7-Day Safety Report | SP874 | | 2006-00418 | 124701/80223 |
| 26-Oct-06 | 0298 | | Follow-up Safety Report | SP745 | | 2006-00350 | 101802 |
| 26-Oct-06 | 0299 | | Information Amendment: Clinical | SP755 | A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization | | |
| 02-Nov-06 | 0300 | | Initial Safety Report | SP774 | | 2006-00094 | 114109 |
| 02-Nov-06 | 0301 | | Follow-up Safety Report | SP774 | | 2006-00409 | 122402 |
| 02-Nov-06 | 0301 | | Follow-up Safety Report | SP754 | | 2006-00209 | 14312/80405 |
| 07-Nov-06 | 0302 | | Follow-up Safety Report | SP830 | | 2006-00420 | 105309 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 09-Nov-06 | 0303 | | Follow-up Safety Report | SP830 | | 2006-00278 | 112204 |
| 13-Nov-06 | 0304 | | Follow-up Safety Report | SP830 | | 2006-00129 | 115104 |
| 13-Nov-06 | 0304 | | Follow-up Safety Report | SP874 | | 2006-00418 | 124701/80223 |
| 15-Nov-06 | 0305 | | Follow-up Safety Report | SP830 | | 2006-00438 | 105318 |
| 28-Nov-06 | 0306 | | Follow-up Safety Report | SP830 | | 2006-00438 | 105318 |
| 28-Nov-06 | 0306 | | Follow-up Safety Report | SP874 | | 2006-00403 | 125009/80029 |
| 28-Nov-06 | 0306 | | Follow-up Safety Report | SP874 | | 2006-00418 | 124701/80223 |
| 05-Dec-06 | 0307 | | 7-Day Safety Report | SP874 | | 2006-00472 | 102205/80148 |
| 05-Dec-06 | 0308 | | SB Meeting Minutes | | Submit minutes from 15-NOV-2006 Type A meeting | | |
| 06-Dec-06 | 0309 | | General Correspondence | | Submit IDMC correspondence wherein IDMC informs Schwarz that lacosamide up to 600mg can be allowed in trials of subjects with diabetic peripheral neuropathy | | |
| 11-Dec-06 | 0310 | | 7-Day Safety Report | SP874 | | 2006-00478 | 129704/80308 |
| 19-Dec-06 | 0311 | | Initial Safety Report | SP830 | | 2006-00495 | 114006 |
| 19-Dec-06 | 0312 | | Follow-up Safety Report | SP874 | | 2006-00478 | 129704/80308 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | A45202 | SPM 927: Effect on survival and reproduction of Daphnia magna in a semi-static test over three weeks | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | A45180 | SPM 927: Toxic effects to zebra fish (Brachydanio rerio) in an early-life stage toxicity test | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 699/17 | (14C)-SPM 927: Quantitative whole-body autoradiography following oral and intravenous administration to the pigmented rat | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 8540 | In Vitro Pharmacology: GABA Transaminase Assay – Study of SPM 927 | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 847 | Structure proposal for polar metabolite | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 826 | SPM 927: Metabolite profiling and identification in the mouse, rat and dog | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 699/48 | A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 699/46 | A study of absorption, distribution, metabolism and excretion following oral administration to the mouse | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 699/47 | SPM 927: A study of absorption and excretion following oral administration to the rat | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | Drommer | SPM 927 Light and electron microscopical investigation of liver tissues from study "13-week oral gavage subchronic toxicity of ADD 234037 in rats" | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | F9672 | Evaluation of the neuroprotective efficacy of compound SPM 927 in rat hippocampal slice cultures after OGD, glutamate and staurosporine insult | | |
| 20-Dec-06 | 0313 | | Information Amendment: Pharmacology/Toxicology | 865 | Inhibition of the cytochrome P450 isoenzymes 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 and SPM 12809 | | |
| 21-Dec-06 | 0314 | | Initial Safety Report | SP774 | | 2006-00481 | 112315 |
| 22-Dec-06 | 0315 | | Initial Safety Report | SP874 | | 2006-00488 | 115902/80260 |
| 22-Dec-06 | 0316 | | Follow-up Safety Report | SP874 | | 2006-00472 | 102205/80148 |
| 03-Jan-07 | 0317 | | Initial Safety Report | SP745 | | 2006-00510 | 110718 |
| 03-Jan-07 | 0317 | | Initial Safety Report | SP615 | | 2006-00515 | 10191 |
| 03-Jan-07 | 0318 | | Follow-up Safety Report | SP745 | | 2006-00289 | 108305 |
| 03-Jan-07 | 0319 | | 7-Day Safety Report | SP756 | | 2006-00473 | 15606 |
| 17-Jan-07 | 0320 | | Initial Safety Report | SP774 | | 2007-00013 | 116206 |
| 17-Jan-07 | 0321 | | Follow-up Safety Report | SP874 | | 2006-00488 | 115902/80260 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 17-Jan-07 | 0321 | | Follow-up Safety Report | SP830 | | 2006-00495 | 114006 |
| 17-Jan-07 | 0322 | | 7-Day Safety Report | SP874 | | 2007-00020 | 129506/80472 |
| 17-Jan-07 | 0322 | | 7-Day Safety Report | SP874 | | 2007-00023 | 115702/80415 |
| 24-Jan-07 | 0323 | | Information Amendment: Pharmacology/Toxicology | 031209 | Identification of harkoseride (SPM 927) targets using affinity capture and proteomics technologies | | |
| 24-Jan-07 | 0323 | | Information Amendment: Clinical | SP757 | A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization | | |
| 30-Jan-07 | 0324 | | Follow-up Safety Report | SP874 | | 2007-00023 | 115702/80415 |
| 30-Jan-07 | 0324 | | Follow-up Safety Report | SP745 | | 2006-00510 | 110718 |
| 30-Jan-07 | 0325 | | 7-Day Safety Report | SP874 | | 2006-00464 | 126603/80275 |
| 08-Feb-07 | 0326 | | Initial Safety Report | SP774 | | 2007-00029 | 116205 |
| 12-Feb-07 | 0327 | | 7-Day Safety Report | SP745 | | 2007-00055 | 175516 |
| 12-Feb-07 | 0327 | | 7-Day Safety Report | SP745 | | 2007-00048 | 100806 |
| 12-Feb-07 | 0328 | | Follow-up Safety Report | SP874 | | 2006-00464 | 126603/80275 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 12-Feb-07 | 0328 | | Follow-up Safety Report | SP615 | | 2006-00515 | 2006-00515 |
| 20-Feb-07 | 0329 | | 7-Day Safety Report | SP746 | | 2007-00068 | 102802 |
| 20-Feb-07 | 0330 | | Initial Safety Report | SP745 | | 2007-00061 | 108703 |
| 20-Feb-07 | 0330 | | Initial Safety Report | SP746 | | 2007-00066 | 125012 |
| 20-Feb-07 | 0331 | | Follow-up Safety Report | SP874 | | 2007-00020 | 129506/80472 |
| 23-Feb-07 | 0332 | | 7-Day Safety Report | SP745 | | 2007-00076 | 170801 |
| 23-Feb-07 | 0332 | | 7-Day Safety Report | SP830 | | 2007-00074 | 116001 |
| 23-Feb-07 | 0332 | | 7-Day Safety Report | SP746 | | 2007-00056 | 110804/80106 |
| 23-Feb-07 | 0333 | | Follow-up Safety Report | SP874 | | 2006-00464 | 126603/80275 |
| 27-Feb-07 | 0334 | | Follow-up Safety Report | SP615 | | 2003-00367 | 11776 |
| 27-Feb-07 | 0334 | | Follow-up Safety Report | SP746 | | 2007-00068 | 102802 |
| 05-Mar-07 | 0335 | | Follow-up Safety Report | SP830 | | 2007-00074 | 116001 |
| 12-Mar-07 | 0336 | | 7-Day Safety Report | SP874 | | 2007-00088 | 121012/80641 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 14-Mar-07 | 0337 | | Information Amendment: Clinical | SP640 | A double-blind, single-site, randomized, placebo- and positive-controlled, parallel-design trial of the electrocardiographic effects of 400 and 800mg per day of lacosamide in healthy male and female subjects: a thorough QT trial | | |
| 19-Mar-07 | 0338 | | General Correspondence | | Request comment on plan to submit integrated safety datasets for all patients in phase 2b/3 trials | | |
| 20-Mar-07 | 0339 | | Initial Safety Report | SP774 | | 2006-00319 | 124611 |
| 20-Mar-07 | 0340 | | Follow-up Safety Report | SP830 | | 2006-00420 | 105309 |
| 20-Mar-07 | 0340 | | Follow-up Safety Report | SP874 | | 2006-00488 | 115902/80260 |
| 23-Mar-07 | 0341 | | General Correspondence | SP906 | Updated cardiovascular safety report | | |
| 26-Mar-07 | 0342 | | 7-Day Safety Report | SP874 | | 2007-00100 | 101408/80363 |
| 26-Mar-07 | 0343 | | Follow-up Safety Report | SP746 | | 2007-00066 | 125012 |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | IS-4-2311 Adden | Addendum to the study report: the early evaluation of anticonvulsant drugs | | |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | 05.673/4 | Evaluation of SPM 927 for abuse potential using an i.v. self-administration paradigm in the rat | | |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | C13703 | The effects of lacosamide in an animal model for migraine | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | Morrow | Harkoseride in pre-clinical animal models of pain | | |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | 05.264/2 | Pseudo-isobolographic evaluation in combination with 5 other analgesic substances using the formalin (late phase) test in the rat (i.p. administration) | | |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | 05.237/5 | Evaluation of SPM 927 as a discriminative stimulus in a drug discrimination procedure in the rat | | |
| 04-Apr-07 | 0344 | | Information Amendment: Pharmacology/Toxicology | 'B-PDG-2006-52 | UV/VIS-absorption of O-desmethyl-lacosamide (SPM 12809) | | |
| 13-Apr-07 | 0345 | | Follow-up Safety Report | SP874 | | 2007-00088 | 121012/80641 |
| 13-Apr-07 | 0345 | | Follow-up Safety Report | SP745 | | 2007-00061 | 108703 |
| 17-Apr-07 | 0346 | | Response to FDA Request for Information | SP640 | Submit SP640 data in response to 22-MARCH-2007 email request from Malandro | | |
| 23-Apr-07 | | | 7-Day Safety Report Fax | SP745 | | 2005-00835 | 174203 |
| 23-Apr-07 | 0347 | | 7-Day Safety Report | SP745 | | 2005-00835 | 174203 |
| 23-Apr-07 | 0348 | | Initial Safety Report | SP756 | | 2006-00422 | 17407 |
| 23-Apr-07 | 0349 | | Follow-up Safety Report | SP615 | | 2003-00367 | 11776 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 24-Apr-07 | 0350 | | Information Amendment: Clinical | SP754 | A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (400 and 600 mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization | | |
| 27-Apr-07 | | | Safety Report Fax | SP830 | | 2006-00098 | 115110 |
| 27-Apr-07 | 0351 | | 7-Day Safety Report | SP830 | | 2006-00098 | 115110 |
| 03-May-07 | 0352 | | Follow-up Safety Report | SP874 | | 2007-00100 | 101408/80363 |
| 09-May-07 | 0353 | | Initial Safety Report | SP756 | | 2007-00140 | 14308 |
| 09-May-07 | 0354 | | Follow-up Safety Report | SP830 | | 2006-00098 | 115110 |
| 09-May-07 | 0354 | | Follow-up Safety Report | SP745 | | 2006-00510 | 110718 |
| 09-May-07 | 0355 | | Information Amendment: Pharmacology/Toxicology | 977 | Metabolite turnover of SPM 927, SPM 6912 and SPM 12809 in S9 fractions obtained from male rat and human livers | | |
| 09-May-07 | 0355 | | Information Amendment: Pharmacology/Toxicology | 1000 | Profiling of polar metabolite | | |
| 16-May-07 | 0356 | | Request FDA Comment | raft, LPT 20614/( | Request for FDA review and comment and teleconference to discuss Division's response | | |
| 17-May-07 | 0357 | | General Correspondence | SP754, SP756 | Submit follow up information in response to 04-MAY-2007 email from Lana Chen, FDA | 000#5#2006-00422 | 17407 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 21-May-07 | | | 7-Day Safety Report Fax | SP745 | | 2005-00463 | 176213 |
| 21-May-07 | 0358 | | 7-Day Safety Report | SP745 | | 2005-00463 | 176213 |
| 21-May-07 | 0359 | | Follow-up Safety Report | SP745 | | 2006-00510 | 110718 |
| 22-May-07 | 0360 | | Follow-up Safety Report | SP756 | | 2006-00442 | 17407 |
| 07-Jun-07 | 0361 | | 7-Day Safety Report | SP745 | | 2007-00155 | 109133 |
| 21-Jun-07 | | | General Correspondence | | Email Ms. Griffis, FDA, plan to submit one all-inclusive NDA under one NDA number | | |
| 22-Jun-07 | 0362 | | Initial Safety Report | SP874 | | 2007-00119 | 124413/80424 |
| 25-Jun-07 | 0363 | | Annual Report | | For the period 26-MAR-2006 through 25-MAR-2007 | | |
| 27-Jun-07 | 0364 | | Information Amendment: Clinical | SP746 subtrial | A double-blind, randomized withdrawal of lacosamide in subjects with painful diabetic neuropathy - subtrial to SP746 | | |
| 06-Jul-07 | 0365 | | 7-Day Safety Report | SP746 | | 2007-00199 | 124902 |
| 06-Jul-07 | 0366 | | Initial Safety Report | SP774 | | 2007-00201 | 106404 |
| 06-Jul-07 | 0367 | | General Correspondence | | | | |
| 12-Jul-07 | 0368 | | Initial Safety Report | SP746 | | 2007-00203 | 101208 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 13-Jul-07 | | | FDA Phone Contact | | Discuss proposed schematic of NDA/eCTD organization and obtain updated status of juvenile toxicology protocol review | | |
| 19-Jul-07 | 0369 | | 7-Day Safety Report | SP746 | | 2007-00214 | 105622 |
| 20-Jul-07 | 0370 | | Response to FDA Request for Information | | Submit additional information request by Ms. Griffis regarding proposed trade name submission | | |
| 23-Jul-07 | | | FDA Phone Contact | | Ms. Griffis, FDA, called on behalf of DMETS to request additional information on trade name review submission | | |
| 23-Jul-07 | | | FDA Correspondence | | Ms. Griffis, FDA, emails comments from nonclinical team regarding draft protocol for juvenile dog toxicity study | | |
| 30-Jul-07 | 0371 | | 7-Day Safety Report | SP830 | | 2007-00230 | 105806 |
| 30-Jul-07 | 0372 | | Follow-up Safety Report | SP745 | | 2005-00835 | 174203 |
| 06-Aug-07 | 0373 | | Follow-up Safety Report | SP830 | | 2007-00074 | 116001 |
| 08-Aug-07 | 0374 | | Initial Safety Report | SP746 | | 2007-00231 | 118301 |
| 14-Aug-07 | 0375 | | 7-Day Safety Report | SP615 | | 2005-00465 | 10477 |
| 15-Aug-07 | 0376 | | 7-Day Safety Report | SP746 | | 2007-00244 | 102717 |
| 15-Aug-07 | 0376 | | 7-Day Safety Report | SP830 | | 2007-00248 | 114211 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 15-Aug-07 | 0376 | | 7-Day Safety Report | SP745 | | 2007-00246 | 110907 |
| 20-Aug-07 | 0377 | | 7-Day Safety Report | SP830 | | 2005-00618 | 105019 |
| 21-Aug-07 | 0378 | | Initial Safety Report | SP774 | | 2006-00066 | 124406 |
| 21-Aug-07 | 0379 | | Follow-up Safety Report | SP746 | | 2007-00231 | 118301 |
| 21-Aug-07 | 0379 | | Follow-up Safety Report | SP746 | | 2007-00199 | 124902 |
| 23-Aug-07 | 0380 | | Information Amendment: Clinical | SP903 | Single-site, randomized, double-blind, placebo- and active comparator controlled single-dose crossover trial to evaluate the abuse potential of lacosamide in healthy subjects with a history of recreationaly CNS depressant use | | |
| 27-Aug-07 | 0381 | | Follow-up Safety Report | SP746 | | 2007-00199 | 124902 |
| 27-Aug-07 | 0381 | | Follow-up Safety Report | SP746 | | 2007-00244 | 102717 |
| 27-Aug-07 | 0381 | | Follow-up Safety Report | SP830 | | 2007-00248 | 114211 |
| 28-Aug-07 | 0382 | | 7-Day Safety Report | SP745 | | 2007-00255 | 108222 |
| 04-Sep-07 | 0383 | | Follow-up Safety Report | SP746 | | 2007-00203 | 101208 |
| 07-Sep-07 | 0384 | | 7-Day Safety Report | SP745 | | 2007-00265 | 102202 |
| 07-Sep-07 | 0385 | | Follow-up Safety Report | SP830 | | 2007-00248 | 114211 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 07-Sep-07 | 0385 | | Follow-up Safety Report | SP830 | | 2007-00248 | 105019 |
| 12-Sep-07 | 0386 | | Follow-up Safety Report | SP746 | | 2007-00214 | 105622 |
| 12-Sep-07 | 0386 | | Follow-up Safety Report | SP830 | | 2007-00248 | 114211 |
| 12-Sep-07 | 0386 | | Follow-up Safety Report | SP615 | | 2005-00465 | 10477 |
| 04-Oct-07 | 0387 | | Initial Safety Report | SP746 | | 2007-00281 | 101707 |
| 15-Oct-07 | 0388 | | 7-Day Safety Report | SP615 | | 2007-00289 | 10180 |
| 16-Oct-07 | 0389 | | Initial Safety Report | SP756 | | 2007-00295 | 15405 |
| 19-Oct-07 | 0390 | | Initial Safety Report | SP745 | | 2007-00288 | 114721 |
| 19-Oct-07 | 0391 | | Information Amendment: Clinical | | Investigator's Brochure dated 31-AUG-2007 | | |
| 25-Oct-07 | 0392 | | Initial Safety Report | SP615 | | 2007-00292 | 11429 |
| 30-Oct-07 | 0393 | | Follow-up Safety Report | SP756 | | 2007-00295 | 15405 |
| 01-Nov-07 | 0394 | | 7-Day Safety Report | SP746 | | 2007-00308 | 105621 |
| 01-Nov-07 | 0395 | | Initial Safety Report | SP774 | | 2006-00439 | 100804 |
| 12-Nov-07 | 0396 | | Initial Safety Report | 10053 | | 2007-00316 | SP615 |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 14-Nov-07 | 0397 | | Initial Safety Report | | | 2007-00317 | 101904 |
| 15-Nov-07 | 0398 | | General Correspondence | | Appointment of UCB as agent in safety reporting to the IND | | |
| 04-Dec-07 | 0401 | | Follow-up Safety Report | | | 2007-00316 | 10053 |
| 04-Dec-07 | 0402 | | Follow-up Safety Report | | | 2007-00288 | 114721 |
| 05-Dec-07 | 0403 | | Protocol Amendment: New Protocol | SP925 | Original Protocol | | |
| 20-Dec-07 | 0407 | | General Correspondence | LPT 20615 | Request FDA concurrence on proposed dosing increase | | |
| 28-Feb-08 | | | General Correspondence | | Email Ms. Ware, FDA, proposed language for updating Informed Consent based on the FDA Alert for suicidality and antieleptic drugs | | |
| 20-Mar-08 | 0417 | | Protocol Amendment: New Investigator | SP925 | New investigator | | |
| 01-Apr-08 | | | General Correspondence | | Email Ware that revised Informed Consent language will be distributed to all lacosamide INDs | | |
| 01-Apr-08 | | | FDA Correspondence | | Ware emails Division's response to proposed Informed Consent language | | |
| 20-May-08 | 0420 | | Protocol Amendment: New Investigator | SP925 | New investigators | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | F-9945 | Differential block of sensory neuronal voltage-gated sodium channels by lacosamide, lidocaine and carbamazepine. (Previously: Effect of lacosamide on recombinant Nav 1.3 and Nav 1.7 voltage-gated sodium current properties) | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | LPT 20614/06 | 6-Week Dose-Range-Finding Study for a 33-Week Chronic Toxicity Study of SPM 927 by Repeated Oral Administration to Juvenile Beagle Dogs | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | 0699/069 | (14C)-SPM 927: A study of absorption and excretion following single oral administration to the rabbit | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | 847 Amend 1 | Structure proposal for polar metabolite | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | 9496 | Oxford Cardiac Pharmacology Ltd: Effect of lacosamide on action potential parameters (including Vmax, the maximal rate of rise) in guinea pig ventricular myocytes | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | MD-11-011-0012 | Evaluation of potential effect of Lacosamide in the acute experimental allergic encephalomyelitis rat model | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | F-9938 | Effect of lacosamide on slow inactivation in Nav 1.2 (expressed in CHO cells) Nav 1.4 and Nav 1.4 and Nav 1.4/IFM>QQQ (expressed in Xenopus oocytes) | | |

| Submission Date | Serial No | Location | Submission Type | Study No | Title/ Description | CIOMS Mfr Control No | CIOMS Subject No |
|---|---|---|---|---|---|---|---|
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | SCHW 004 | Evaluation of Lacosamide in an animal model for obsessive compulsive disorder: marble burying | | |
| 28-May-08 | 0422 | | Information Amendment: Pharmacology/Toxicology | F-9928 | Determination of interaction of lacosamide with the antiepileptic drugs carbamazepine, Phenytoin, sodium valproate, lamotrigine, levetiracetam, topiramate and gabapentin | | |
| 24-Jun-08 | 0424 | | Annual Report | | Period covering March 26, 2007 through March 25, 2008 | | |
| 20-Aug-08 | 0425 | | Protocol Amendment: New Investigator | SP925 | New investigators | | |
| 09-Oct-08 | 0431 | | Protocol Amendment: Change in Protocol | SP925 | Amendment 1 | | |

# *NDA 22-254 Submissions*

| *Date* | *Serial No* | *Submission Type* | *Study No* | *Title of Report* |
|---|---|---|---|---|
| 28-Sep-07 | 0000 | Original NDA | | |
| 20-Nov-07 | | FDA Correspondence | | Ms. Ware, FDA, emails request from clinical pharmacology group related to initial filing review of the lacosamide applications |
| 26-Nov-07 | 0001 | Response to FDA Request for Inf | | Submit response to 20-NOV-2007 clinical pharmacology request |
| 10-Dec-07 | | FDA Correspondence | | Dr. Katz, FDA, sends letter accepting NDA for filing |
| 13-Dec-07 | | Amendment to a Pending Applicat | | Submit additional clinical pharmacology responses |
| 13-Dec-07 | 0002 | Amendment to a Pending Applicat | | Response to request: clinical pharmacology; provide responses not included in 0001 |
| 19-Dec-07 | | General Correspondence | | Email Ms. Ware, FDA, preliminary responses to 74-day letter |
| 07-Jan-08 | | FDA Correspondence | | Ms. Ware, FDA, emails request from clinical and statistical team for additional datasets |
| 07-Jan-08 | | General Correspondence | | Email Ms. Ware, FDA, that requested datasets were sent on DVD via courier |
| 14-Jan-08 | | FDA Correspondence | | Ms. Ware, FDA, emails requests from DNP's clinical team related to ongoing review of lacosamide applications |
| 15-Jan-08 | | General Correspondence | | Email Ms. Ware, FDA, for additional explanation on clinical questions received 14-JAN-2008 |
| 15-Jan-08 | | FDA Correspondence | | Ms. Ware, FDA, emails responses from email information request related to 14-JAN-2008 FDA email |
| 16-Jan-08 | | General Correspondence | | Email Ms. Ware, FDA, summary of 16-JAN-2008 conversation discussing GCP inspections |
| 16-Jan-08 | | FDA Correspondence | | Mr. Sullivan, FDA, emails outstanding clinical pharmacology items |
| 17-Jan-08 | | FDA Correspondence | | Ms. Gunther, FDA, emails information request for potential inspection sites |
| 23-Jan-08 | 0003 | Amendment to a Pending Applicat | | 120-day safety update and 74-day letter responses |
| 29-Jan-08 | | FDA Correspondence | | Ware emails request form DNP's clinical team for a summary table of AE that led to dose reduction and/or discontinuation by SOC and PT in Pool EP S1 by dose at onset |

| Date | Serial No | Submission Type | Study No | Title of Report |
|---|---|---|---|---|
| 31-Jan-08 | | FDA Correspondence | | Ms. Ware, FDA, emails request from DNP's clinical team |
| 04-Feb-08 | | FDA Correspondence | | Ms. Mercado, FDA, emails request for confirmation for FDA inspection of NDA 22-254 in Germany |
| 06-Feb-08 | | FDA Correspondence | SP742, SP743, SP768 | Sullivan emails request additional analyses for SP742, SP743, and SP768 |
| 07-Feb-08 | | FDA Correspondence | | Sheryl Gunther, FDA, emails request for addresses for investigators Nischik, Pojakovic, and Hajnsek |
| 08-Feb-08 | | General Correspondence | | Email Ms. Gunther, FDA, contact information requested 07-FEB-2008 |
| 08-Feb-08 | | FDA Correspondence | | Ms. Gunther, FDA, emails thanks for contact information |
| 08-Feb-08 | | General Correspondence | | Email Ms. Ware, FDA, partial responses to questions received 14-JAN-2008 and 31-JAN-2008 |
| 08-Feb-08 | | Response to FDA Request for Inf | | Send Ms. Gunther, FDA, background investigator information rquested 17-JAN-2008 |
| 12-Feb-08 | | General Correspondence | | Email Ms. Ware, FDA, additional partial responses to questions received 14-JAN-2008 and 31-JAN-2008 |
| 13-Feb-08 | 0004 | Amendment to a Pending Applicat | | Response to request: clinical; respond to questions received 15-JAN, 29-JAN, and 31-JAN-2008 |
| 14-Feb-08 | | FDA Correspondence | | Ms. Ware, FDA, emails requests from DNP's clinical team |
| 14-Feb-08 | | General Correspondence | | Email Ms. Ware, FDA, that one request from 14-FEB-2008 email is addressed in lifecycle received today and the other will be reviewed |
| 22-Feb-08 | | General Correspondence | | Email Ms. Ware, FDA, responses to request from 14-FEB-2008 email |
| 25-Feb-08 | 0005 | Amendment to a Pending Applicat | | Response to request: clinical; respond to 31-JAN-2008, 06-FEB-2008, and 14-FEB-2008 email requests |
| 26-Feb-08 | | FDA Correspondence | | Ms. Ware emails request from DNP's clinical pharmacology team |
| 03-Mar-08 | | FDA Correspondence | | Ms. Ware, FDA, emails requests from DNP's clinical team |
| 05-Mar-08 | | FDA Correspondence | | Email Ms. Ware, FDA, response to one of the request received 03-MAR-2008 |
| 05-Mar-08 | | General Correspondence | | Email Ms. Ware, FDA, response to request received 26-FEB-2008 |

| Date | Serial No | Submission Type | Study No | Title of Report |
|---|---|---|---|---|
| 06-Mar-08 | | FDA Correspondence | | Sullivan emails request from DAARP team for narratives for all patients with AEs of syncope of presyncope and tables comparing frequence of event by treatment group |
| 07-Mar-08 | | FDA Correspondence | SP754 | Ware emails requests from DNP's clinical team; request additional detail on subject 75411401 and clarification of footnote in cardiac report |
| 07-Mar-08 | | FDA Phone Contact | | Discuss NDA reviews with Ms. Ware, FDA |
| 10-Mar-08 | | General Correspondence | | Email Ms. Ware, FDA, clarification on 03-MAR-2008 request |
| 10-Mar-08 | | Response to FDA Request for Inf | | Submit requested ECG data for subjects in EP Pool S1 |
| 11-Mar-08 | | FDA Correspondence | | Mr. Sullivan emails on behalf of Ms. Ware request for additional analyses |
| 11-Mar-08 | | General Correspondence | | Email Dr. Vallalba and Ms. Ware password for response to request for EP pool S! dataset from ISS |
| 11-Mar-08 | | General Correspondence | | Request Ms. Ware forward 11-MAR-2008 email to Dr. Vallalba |
| 13-Mar-08 | | FDA Correspondence | SP903 | Sullivan emails request from the stats reviewer for clarification on abuse liability study's dataset |
| 20-Mar-08 | 0006 | Amendment to a Pending Applicat | | Response to Request: Clinical; respond to 04-MAR-2008 teleconference request and 13-MAR-2008 email; also respond to email requests 26-FEB-2008, 03-MA$-2008, 07-MAR-2008, 11-MAR-2008; provide draft blister labels and cartons requested in 74-day letter |
| 20-Mar-08 | | FDA Correspondence | | Sullivan emails CMC IR letter that applies to drug substance, tablet, and IV drug product |
| 20-Mar-08 | | FDA Correspondence | | Dr. Sood, FDA, mails information request letter regarding drug substance and drug product |
| 31-Mar-08 | | FDA Correspondence | | Sullivan emails request to resubmit ISS lab1.xpt and lab2.xpt datasets as separate files |
| 02-Apr-08 | | FDA Correspondence | | Ware emails requests from DNP's statistical team |
| 03-Apr-08 | | FDA Correspondence | | Ware emails requests from DNP's statistical team |
| 03-Apr-08 | 0007 | Amendment to a Pending Applicat | | Response to Request: Clinical; respond to 07-MAR-2008 email request for clarification on subject 75411401 and 31-MAR-2008 email request for lab datasets |
| 04-Apr-08 | | General Correspondence | | Email Ware receipt of 04-APR-2008 comments regarding impurity specifications |
| 04-Apr-08 | | General Correspondence | | Email Ware agreement to be available 07-APR-2008 between 1pm and 3pm to discuss internal FDA meeting |

| Date | Serial No | Submission Type | Study No | Title of Report |
|---|---|---|---|---|
| 04-Apr-08 | | FDA Correspondence | | Ware emails that labeling submission next week is acceptable; would like to speak about updates from internal meeting |
| 04-Apr-08 | | FDA Correspondence | | Ware adds additional comment to email sent earlier today |
| 04-Apr-08 | | FDA Correspondence | | Ware emails comments from ONDQA and OND non-clinical review teams related to proposed impurity specifications |
| 04-Apr-08 | | General Correspondence | | Email Ware if there is any update regarding CSS and the tradename and notify that revised label/container cartons will be sent next week |
| 07-Apr-08 | | FDA Correspondence | | Ware emails agreement to clarification on symbol in 04-APR-2008 request |
| 07-Apr-08 | | General Correspondence | | Email Ware clarification on symbol in 04-APR-2008 request |
| 09-Apr-08 | 0008 | Amendment to a Pending Applicat | | Revised labeling - excluding package insert |
| 11-Apr-08 | | General Correspondence | | Email Ware responses to 02-APR-2008 statistical questions |
| 11-Apr-08 | | General Correspondence | | Email Ware responses to questions emailed 04-APR-2008 on drug substance and IV/syrup formulation |
| 14-Apr-08 | 0009 | Amendment to a Pending Applicat | | Response to Request: Clinical; respond to 06-MAR-2008 and 07-MAR-2008 clinical email requests for narratives for all neuropathic pain subjects with syncompe or presyncope; provide narratives for migraine study dropouts as requested in 11-MAR-2007 email |
| 16-Apr-08 | | FDA Correspondence | | Ware emails request from DNP's clinical team regarding overall exposure to lacosamide and placebo in all studies |
| 18-Apr-08 | | Amendment to a Pending Applicat | | Provide responses to requests in CMC letter dated 20-MAR-2008 and emails dated 02-APR-2008 and 04-APR-2008 |
| 18-Apr-08 | | FDA Correspondence | SP755, SP774, SP757 | Ware emails request from DNP's clinical team regarding patients 170106 and 17011 |
| 18-Apr-08 | 0010 | Amendment to a Pending Applicat | | Respond to 20-MAR-2008 CMC request and 02-APR-2008 and 04-APR-2008 email requests |
| 25-Apr-08 | | FDA Correspondence | | Ware emails request from DNP's CMC review team |
| 25-Apr-08 | | FDA Correspondence | | Ware emails request from DNP's clinical team regarding subject 588/8061 |
| 28-Apr-08 | | General Correspondence | | Email Ware Schwarz commitments following 23-APRIL-2008 teleconference regarding oral syrup dosing |

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| 29-Apr-08 | | FDA Correspondence | | Sullivan emails request for narratives of patients with AE dyskinesia |
| 30-Apr-08 | 0011 | Amendment to a Pending Applicat | | Respond to requests received 20-MAR-2008, 16-APR-2008, and 18-APR-2008 |
| 30-Apr-08 | | Response to FDA Request for Inf | 1106 | Email Ware partial response to 25-APRIL-2008 email request regarding CMC data |
| 06-May-08 | | FDA Correspondence | | Sullivan emails request from reviewer of Environmental Assessment to submit a non-confidential EA |
| 07-May-08 | | FDA Correspondence | | Ware emails request from DNP's clinical team requesting narratives and CRFs for four patients who discontinued due to cardiac or ECG issues; ECGs for 755122303; suicidality information on 754/12512 |
| 08-May-08 | | Response to FDA Request for Inf | | Email Ware dyskinesia narratives requested in 29-APRIL-2008 email |
| 09-May-08 | 0012 | Amendment to a Pending Applicat | | Response to requests; respond to nonclinical question in 25-APR-2008 email and provide revision to environmental assessment requested in 06-MAY-2008 email |
| 12-May-08 | | FDA Correspondence | | Ware emails requests from DNP's clinical team |
| 12-May-08 | | General Correspondence | | Email Ware that 12-MAY-2008 requests have been received |
| 12-May-08 | | FDA Correspondence | | Ware emails request from chemistry review team regarding NDA 22-254 and NDA 22-255 |
| 13-May-08 | | Response to FDA Request for Inf | | Email Ware AE report responding to 25-APRIL-2008 email request regarding subject 588-8061 |
| 13-May-08 | | General Correspondence | | Email Ware requested laboratory results for subject 588/5061 |
| 16-May-08 | | Response to FDA Request for Inf | | Email Ware response to questions 2, 3, and 4 from 12-MAY-2008 email request |
| 16-May-08 | | Response to FDA Request for Inf | | Email Ware responses to bullets 1 and 2 from 07-MAY-2008 email request regarding narratives and CRFs and ECG data |
| 16-May-08 | | General Correspondence | | Email Ware question/proposal regarding request number 5 from 12-MAY-2008 email request |
| 16-May-08 | | FDA Correspondence | | Ware emails request from clinical reviewer for clarification on tables EP 5.1.1 and EP 5.1.2 from partial response to 12-MAY-2008 request |
| 19-May-08 | | Response to FDA Request for Inf | | Email Ware partial response to 16-MAY-2008 email request and suggest teleconference if response is not sufficient |
| 19-May-08 | | Response to FDA Request for Inf | | Email Ware response to bullet 3 from 07-MAY-2008 email request regarding subject 754/12512 suicidality |

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| 20-May-08 | | FDA Correspondence | SP643 | Ware emails requests from clinical pharmacology review team regarding SP643 and analytical assay validation methods |
| 21-May-08 | | FDA Correspondence | | Ware emails WORD document of example table for requested summary information on analytical assay validation methods |
| 22-May-08 | | FDA Correspondence | | Ware emails request from clinical review team for additional information on subject 588/8061 |
| 23-May-08 | | General Correspondence | | Email Ware response to 22-MAY-2008 request for information on subject 588/5061 |
| 23-May-08 | | Response to FDA Request for Inf | | Email Ware response to email request received 22-MAY-2008 regarding subject 588/8061 |
| 27-May-08 | | Response to FDA Request for Inf | SP643 | Email Ware responses to clinical pharmacology requests received in 20-MAY-2008 email regarding subject classification in SP643 and analytical assay validation methods |
| 27-May-08 | 0013 | Amendment to a Pending Applicat | | Response to requests in 25-APR-2008, 29-APR-2008, 07-MAY-2008, 12-MAY-2008, 16-MAY-2008, and 22-MAY-2008 emails |
| 30-May-08 | | FDA Phone Contact | | Ware calls to request WORD copy of draft labeling; also discuss review items: scheduling, labels, post-marketing requests, REMS, pediatrics, class labeling |
| 02-Jun-08 | | FDA Correspondence | | Ware emails question about 02-JUNE-2008 response to 12-MAY-2008 question 1 |
| 04-Jun-08 | | General Correspondence | | Email Ware concomitant disease tables requested 12-MAY-2008 |
| 06-Jun-08 | | FDA Correspondence | | Ware emails request for teleconference 12-JUNE-2008 at 10:15 to discuss potential cases of multi-organ hypersensitivity |
| 11-Jun-08 | 0014 | Amendment to a Pending Applicat | | Respond to requests received 12-MAY-2008 and 2-JUN-2008 |
| 11-Jun-08 | | FDA Correspondence | SP830 | Ware emails request for additional information on subject SP830/111201 and request for database search for all cases of potential multiorgan hypersensitivity reactions |
| 26-Jun-08 | | FDA Phone Contact | | Ware calls to discuss review with goal of reaching an actio by 29-JUL-2008, dependent on review of multi-organ hypersensitivity data; also discuss labeling |
| 30-Jun-08 | | Meeting Request | | Type A meeting request to discuss abuse potential of lacosamide |
| 02-Jul-08 | | FDA Correspondence | | Ware emails comments from controlled substance staff with conclusion that lacosamide has abuse potential similar to alprazolam, a schedule IV drug |
| 03-Jul-08 | | General Correspondence | | Email Ware requested documents |
| 10-Jul-08 | | General Correspondence | | Email Ware response to multiorgan hypersensitivity issue raised in 06-JUN-2008 email, 11-JUN-2008 email, and 12-JUN-2008 teleconference |

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| 10-Jul-08 | | General Correspondence | | Email Sullivan to ask when to expect draft labeling from DAARP |
| 11-Jul-08 | | General Correspondence | | Email Ware pediatric development document |
| 11-Jul-08 | 0015 | Amendment to a Pending Applicat | | Response to requests; respond to request in 11-JUN-2008 teleconference to search for cases of multi-organ hypersensitivity based on defined criteria; final part of response to 12-MAY-2008 CMC request; and Type A meeting request |
| 12-Jul-08 | | Response to FDA Request for Inf | | Email Ms. Ripper, FDA, table of enrollment and last subject dates in response to financial disclosure request |
| 12-Jul-08 | | General Correspondence | | Email Leah Ripper, FDA, table showing financial disclosure cutoff dates by trial. |
| 14-Jul-08 | | FDA Correspondence | | Ripper emails that financial disclosure information emailed 12-JUL-2008 addresses her concern |
| 15-Jul-08 | | FDA Correspondence | | Ware emails that DNP and DAARP labeling comments will likely be combined |
| 15-Jul-08 | | General Correspondence | | Ware emails that DAARP and DNP labeling comments will be combined |
| 17-Jul-08 | 0016 | Amendment to a Pending Applicat | | Response to requests; provide case report forms related to 0015 submission |
| 18-Jul-08 | | FDA Phone Contact | | Teleconference to discuss multi-organ hypersensitivity and three month extension of review clock |
| 21-Jul-08 | | General Correspondence | | Email Ms. Ware request for copy of Eight Factor Analsis prepared by CSS to determine lacosamide's scheduling |
| 21-Jul-08 | | General Correspondence | | Email Ware request for copy of full Eight Factor Analysis prepared by CSS |
| 22-Jul-08 | | General Correspondence | | Email Ware requesting discussion on CSS analysis, potential extension of PDUFA date, clinical hold, and safety update |
| 25-Jul-08 | | FDA Correspondence | | Ware emails the Action letter for pain indication should be issued based on the old regulations |
| 25-Jul-08 | | FDA Phone Contact | | SB calls Ware to discuss additional terms for multiorgan hypersensitivity, extension of action date, CSS analysis, safety update, pediatric clinical hold, and draft label |
| 25-Jul-08 | | General Correspondence | | Email Sullivan to ask if Action letter for LCM for pain will be a Complete Response letter or the old style of approvable or not approvable |
| 25-Jul-08 | | FDA Correspondence | | Ware emails list of additional search terms suggestive or internal organ involvement |
| 28-Jul-08 | | General Correspondence | | Email Ware request from medical colleagues for clarity on inclusion of preferred terms hepatitis and hypersensitivity in multiorgan hypersensitivity analysis |

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| 28-Jul-08 | | FDA Correspondence | | Sare Stradley emails "Not Approvable" letter for 22-284 |
| 29-Jul-08 | | FDA Correspondence | | Stradley emails that FDA will be in touch about scheduling meeting requested 29-JUL-2008 |
| 29-Jul-08 | | General Correspondence | | Email Ware and Sullivan lifecycle 0017, response to 22-284 action letter received 28-JUL-2008, meeting request, and request for extension of review period |
| 30-Jul-08 | 0017 | Amendment to a Pending Applicat | | Request for extension of review period; meeting request |
| 30-Jul-08 | | General Correspondence | | Email Ware supporting data for subject 588/8061 where the bilirubin value was normal |
| 31-Jul-08 | | FDA Correspondence | | Ware emails request for laboratory value critieria clarification |
| 31-Jul-08 | | FDA Correspondence | | Nighswander mails PDUFA extension letter for epilepsy indications |
| 01-Aug-08 | | FDA Correspondence | | Ware emails request from DNP's clinical team to clarify the denominators used in the search for potential multi-organ hypersensitivity |
| 01-Aug-08 | 0018 | Amendment to a Pending Applicat | | Response to requests; provide proposed questions for Type A meeting requested 30-JUN-2008; provide location of CRF data for subject 588/8061; submit high level pediatric development plan |
| 04-Aug-08 | | FDA Phone Contact | | Stradley calls to discuss meeting on Not Approvable letter for the pain indication |
| 06-Aug-08 | | FDA Correspondence | | Sullivan emails that 22-284 meeting request is considered a Type A meeting but usually can't be granted in requested time frame |
| 06-Aug-08 | | FDA Correspondence | | Ware emails comments from Controlled Substance Staff in response to 31-JUL-2008 request |
| 07-Aug-08 | | General Correspondence | | Email Ware clarification question on CSS analysis |
| 11-Aug-08 | | General Correspondence | | Email Ware requesed normal lab values for subject 588/8061 |
| 14-Aug-08 | 0019 | Amendment to a Pending Applicat | | Response to requests; respond to 18-JUL2008 teleconference and 25-JUL and 31-JUL email requests for addition of search terms and criteria to multi-organ hypersensitivity search; provide normal lab values for subject 588/8061 as requested 31-JUL-2008 |
| 19-Aug-08 | | General Correspondence | | Email Ware questions regarding meeting package to be sent for 29-SEP-2008 meeting |
| 19-Aug-08 | | General Correspondence | | Email Ware request for cardiac section of the draft label and question on pediatric drug development |
| 21-Aug-08 | | General Correspondence | | Email Ware response to 01-AUG-2008 request for multi-organ hypersensitivity information |

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| 21-Aug-08 | | FDA Phone Contact | | Discussion of meeting with DNP/CSS on scheduling and to discuss responses to questions previously asked |
| 27-Aug-08 | 0020 | Amendment to a Pending Applicat | | Response to requests; respond to 01-AUG-2008 email request for clarification on multi-organ hypersensitivity reaction denominators; provide revised blister labels |
| 04-Sep-08 | 0021 | Meeting Package | | Information package for Type A meeting on September 29, 2008 |
| 10-Sep-08 | | General Correspondence | | Email Ware that response to multi-organ hypersensitivity request was sent as life cycle 19 on 14-AUG-2008 |
| 23-Sep-08 | 0022 | Amendment to a Pending Applicat | | Meeting Package for Type A meeting on October 16, 2008 |
| 26-Sep-08 | | General Correspondence | | Email Sullivan letter from Schwarz to EMEA withdrawing the lacosamide pain application |
| 26-Sep-08 | | FDA Correspondence | | Ware emails Agency's preliminary responses to questions for 29-SEP-2008 meeting |
| 29-Sep-08 | | FDA Correspondence | | Sullivan emails that 15 desk copies will be required for 16-OCT-2008 meeting package |
| 30-Sep-08 | | General Correspondence | | Email Sullivan that meeting package for 16-OCT-2008 meeting will be sent via email today and as a lifecycle tomorrow, 01-OCT-2008 |
| 01-Oct-08 | | FDA Correspondence | | Sullivan emails thanks for PDF of 16-OCT-2008 meeting package and provides mailing address for desk copies |
| 03-Oct-08 | | FDA Correspondence | | Ware emails list of FDA attendees from 29-SEP-2008 meeting |
| 08-Oct-08 | | General Correspondence | | Email Ware meeting minutes and meeting slides from 29-SEP-2008 meeting with DNP and CSS |
| 10-Oct-08 | | General Correspondence | | Email Ware letter from Patty Fritz requesting teleconference to discuss scheduling |
| 14-Oct-08 | | FDA Correspondence | | Dr. Throckmorton emails to notify that Agency is discussing how best to handle teleconference requested 10-OCT-2008 |
| 15-Oct-08 | 0023 | Amendment to a Pending Applicat | | Reply to FDA preliminary response to questions submitted in life cycle 0021 concerning CSS recommendations of C-IV scheduling |
| 15-Oct-08 | 0023 | Amendment to a Pending Applicat | | Reply to FDA preliminary response to questions submitted in life cycle 0021 concerning CSS recommendations of C-IV scheduling |
| 17-Oct-08 | | General Correspondence | | Email Ware proposed REMS form |
| 21-Oct-08 | | FDA Phone Contact | | Ware returned call to discuss isses from label review, including storage conditions, safety pharmacology section, CSS class, suicidality, and post-marketing commitments |

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| 21-Oct-08 | 0024 | Amendment to a Pending Applicat | | Proposed REMS |
| 21-Oct-08 | 0024 | Amendment to a Pending Applicat | | Proposed REMS |
| 23-Oct-08 | | FDA Correspondence | | Ware emails post-marketing commitments and labeling revisions |
| 23-Oct-08 | | General Correspondence | | Email Ware response to Division label changes and proposals for consideration as well as a justification document for the sponsor-requested changes |
| 27-Oct-08 | | General Correspondence | | Email Ware analysis requested at 27-OCT-2008 meeting for PR outliers |
| 29-Oct-08 | | FDA Correspondence | | Ware emails complete response letter for 22-255 and approval letter for 22-253 and 22-254 |
| 30-Oct-08 | 0025 | Amendment to a Pending Applicat | SP903 | Response to request; additional information requested in 20-OCT-2008 teleconference by Dr. Throckmorton from SP903, abuse liability trial |
| 30-Oct-08 | 0025 | Amendment to a Pending Applicat | SP903 | Response to request; additional information requested in 20-OCT-2008 teleconference by Dr. Throckmorton from SP903, abuse liability trial |